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Main Menu | Search Form | Posting Counts | Show S Numbers | Edit S Numbers | Preferences

Search Results -

Terms	Documents
telomerase near (antisense or ribozyme)	19

Database: US Patents Full-Text Database; US Pre-Grant Publication Full-Text Database; JPO Abstracts Database; EPO Abstracts Database; Derwent World Patents Index; IBM Technical Disclosure Bulletins

Refine Search: telomerase near (antisense or ribozyme) Clear

Search History

Today's Date: 4/5/2001

DB Name	Query	Hit Count	Set Name
USPT,PGPB,JPAB,EPAB,DWPI	telomerase near (antisense or ribozyme)	19	L3
DWPI	telomerase near (antisense or ribozyme)	3	L2
USPT,PGPB,JPAB,EPAB,DWPI	telomerase and (antisense or ribozyme)	140	L1

```
Logging in to Dialog

Trying 3106900061...Open

DIALOG INFORMATION SERVICES
PLEASE LOGON:
 ********
ENTER PASSWORD:
□t840lcpq
 ********
Welcome to DIALOG

Dialog leel 00.12.12D

Lat logoff:  26mar01 12:19:32
Logon file001 05apr01 19:57:19
           *** ANNOUNCEMENT ***
                  ***
NEW FILE RELEASED
***IBISWorld Market Reearch (File 753)
***Inetext PDF Index (File 745)
***Dail and Snda Telegraph (London) Paper (File 756)
***The Mirror Grop Pblication (United Kingdom) (File 757)
***Reter Bine Inight (File 759)

UPDATING RESUMED
***Extel Financial Card from Primark (File 500)
***Book In Print (File 470)
***Extel New Card from Primark (File 501)
                           ***
RELOADED
***Kompa Aia/Pacific (File 592)
***Kompa Central/Eatern Erope (File 593)
***Kompa Canada (File 594)

FILES REMOVED
□dialog
***EconBase (File 565)

New pricing structure for Pharmaprojects (Files 128/928) from
April 1, 2001. Check Help News128 or Help News928 for further
information.

>>>Get immediate news with Dialog's First Release
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   OneSearch simply BEGIN FIRST for coverage from Dialog's
   broad spectrum of news wires.

     >>> Enter BEGIN HOMEBASE for Dialog Announcements <<<
     >>>    of new databases, price changes, etc.      <<<
                  ****
****                              *****

File   1:ERIC  1966-2001/Mar 27
       (c) format only 2001 The Dialog Corporation
```

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      Set  Items  Description
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? b 410

>>>'IALOG' not recognized as set or accession number
? set hi ;set hi

       05apr01 19:57:25 User233835 Session D490.1
            $0.43    0.123 DialUnits File1
     $0.43  Estimated cost File1
     $0.05  TYMNET
     $0.48  Estimated cost this search
     $0.48  Estimated total session cost   0.123 DialUnits

File 410:Chronolog(R)  1981-2001 Jan/Feb
       (c) 2001 The Dialog Corporation

      Set  Items  Description
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?
HILIGHT set on as ''
HILIGHT set on as ''
? b 155, 5, 357

       05apr01 19:57:37 User233835 Session D490.2
            $0.00    0.058 DialUnits File410
     $0.00  Estimated cost File410
     $0.01  TYMNET
     $0.01  Estimated cost this search
     $0.49  Estimated total session cost   0.180 DialUnits

SYSTEM:OS  - DIALOG OneSearch
  File 155:MEDLINE(R)  1966-2000/Dec W4
         (c) format only 2000 Dialog Corporation
*File 155: Further to NLM notification, Medline updating is expected
to resume in March 2001. For other NLM information see Help News155.
  File   5:Biosis Previews(R)  1969-2001/Mar W4
         (c) 2001 BIOSIS
  File 357:Derwent Biotechnology Abs  1982-2001/Mar B2
         (c) 2001 Derwent Publ Ltd
*File 357: Price changes as of 1/1/01. Please see HELP RATES 357.

      Set  Items  Description
      ---  -----  -----------
? e au=kealey, j


Ref   Items  Index-term
E1        7  AU=KEALEY WD
E2        1  AU=KEALEY WF
E3        0 *AU=KEALEY, J
E4        1  AU=KEALHEIM G
E5        2  AU=KEALHOFER L
E6        1  AU=KEALHOFER L K
E7        3  AU=KEALHOFER LISA
E8        3  AU=KEALIHER A
E9        1  AU=KEALIHER AYNSLEY
E10       7  AU=KEALL A
E11       2  AU=KEALL C L
E12       2  AU=KEALL CL

          Enter P or PAGE for more
? e au=kealey, james
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E1        7  AU=KEALEY WD
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E3        0 *AU=KEALEY, JAMES
E4        1  AU=KEALHEIM G
E5        2  AU=KEALHOFER L
E6        1  AU=KEALHOFER L K
E7        3  AU=KEALHOFER LISA
E8        3  AU=KEALIHER A
E9        1  AU=KEALIHER AYNSLEY
E10       7  AU=KEALL A
E11       2  AU=KEALL C L
E12       2  AU=KEALL CL

          Enter P or PAGE for more
? e au=pruzan, r


Ref   Items  Index-term
E1        5  AU=PRUZAN-HOTCHKISS A
E2        1  AU=PRUZAN-HOTCHKISS ANITA
E3        0 *AU=PRUZAN, R
E4        1  AU=PRUZANDKY JJ
E5        1  AU=PRUZANSKI S
E6      439  AU=PRUZANSKI W
E7        1  AU=PRUZANSKI W R
E8       27  AU=PRUZANSKI WALDEMAR
E9        1  AU=PRUZANSKI WR
E10       1  AU=PRUZANSKY D
E11       1  AU=PRUZANSKY E
E12      15  AU=PRUZANSKY J

          Enter P or PAGE for more
? e au=weinrich, S


Ref   Items  Index-term
E1       33  AU=WEINRICH W
E2        1  AU=WEINRICH WOLFGANG
E3        0 *AU=WEINRICH, S
E4        2  AU=WEINRICK BRIAN
E5        7  AU=WEINRIEB I J
E6        6  AU=WEINRIEB IJ
E7        4  AU=WEINRIEB R
E8        1  AU=WEINRIEB R M
E9        6  AU=WEINRIEB RM
E10       1  AU=WEINRIEB ROBERT
E11       2  AU=WEINRIEB ROBERT M
E12       4  AU=WEINRIEB S

          Enter P or PAGE for more
? e au=weinrich, Scot


Ref   Items  Index-term
E1       33  AU=WEINRICH W
E2        1  AU=WEINRICH WOLFGANG
E3        0 *AU=WEINRICH, SCOT
E4        2  AU=WEINRICK BRIAN
E5        7  AU=WEINRIEB I J
E6        6  AU=WEINRIEB IJ
E7        4  AU=WEINRIEB R
E8        1  AU=WEINRIEB R M
E9        6  AU=WEINRIEB RM
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E10        1  AU=WEINR     ROBERT
E11        2  AU=WEINR     ROBERT M
E12        4  AU=WEINRIEB S

           Enter P or PAGE for more
? logoff

       05apr01 19:59:47 User233835 Session D490.3
             $0.16    0.050 DialUnits File155
      $0.16  Estimated cost File155
             $0.91    0.162 DialUnits File5
      $0.91  Estimated cost File5
             $2.20    0.174 DialUnits File357
      $2.20  Estimated cost File357
             OneSearch, 3 files,  0.386 DialUnits FileOS
      $0.15  TYMNET
      $3.42  Estimated cost this search
      $3.91  Estimated total session cost   0.566 DialUnits
Logoff: level 00.12.12 D  19:59:47
```

8 9 tt 8 8 9 t

Trying 9158046...Open

box200> enter system id

Logging in to Dialog

DIALOG INFORMATION SERVICES
PLEASE LOGON:
 ****
IALOG Invalid account number

DIALOG INFORMATION SERVICES
PLEASE LOGON:
 ****
ENTER PASSWORD:
 t840lcpq
 ****
Welcome to DIALOG

Dialog level 98.01.01D

Last logoff: 09feb98 17:56:53
Logon file001 10feb98 17:15:51
ANNOUNCEMENT **** ANNOUNCEMENT **** ANNOUNCEMENT
NEW
***TableBase (File 93)
***U.S. Newswire (File 605)
***OneSearch REPORT TITLES available in Market Research Files
***DIALOG Direct(SM) Launched!
                          ***
RELOADS
***Derwent Patent Citation Index, File 342, now updating
***Medline, Files 154,155
***BioCommerce Abstracts and Directory, File 286
***IMSWorld Patents International, Files 447 and 947
***CLAIMS/U.S. PATENTS (File 340): The complete patent collection
   is now in a single file (Dialog File 340) which incorporates
   the following discontinued CLAIMS files: 125,23,24,25. Updates
   are now weekly.
***CLAIMS/UNITERM (File 341) now incorporates the following
   discontinued CLAIMS files: 223,224,225.
***CLAIMS/COMPREHESIVE (File 942) now incorporates the following
   discontinued files: 923,924,925.
                          ***
FORMAT CHANGES
***Derwent World Patents Index (Files 351/352) display
   formats have changed. See HELP NEWS351.
                          ***
REMOVED
***American Statistics Index, File 102, Removed February 1
                          ***
DIALOG ONDISC(TM)
***New Dialog OnDisc(TM): British Education Index
                          ***
UPDATE '98
***Early bird registration discount extended. Register before
   January 31 and pay only $199. April 15-17 in Philadelphia.

```
                              ***
PRICE CHANGES
***Prices have been adjusted in a number of Dialog databases
   as of January 1. Updated price list is available via
   ASAF (document numbers 5008-5011) and on the Web at
   http://phoenix.dialog.com/products/dialog/dial_pricing.html.

     >>> Enter BEGIN HOMEBASE for Dialog Announcements <<<
     >>>    of new databases, price changes, etc.      <<<
     >>>    Announcements last updated    2Feb98       <<<
* * * New CURRENT year ranges installed.* * *


File   1:ERIC  1966-1997/Dec
       (c) format only 1998 The Dialog Corporation

      Set  Items  Description
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? b 410

       10feb98 17:15:57 User233835 Session D68.1
            $0.03    0.001 Hrs File1
     $0.03  Estimated cost File1
     $0.03  Estimated cost this search
     $0.03  Estimated total session cost   0.001 Hrs.

File 410:Chronolog(R)  1981-1998/Jan
       (c) 1998 The Dialog Corporation plc

      Set  Items  Description
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? set hi ;set hi

HILIGHT set on as ''
HILIGHT set on as ''
? b 5, 155, 357, 399, 351, 653, 654

       10feb98 17:16:29 User233835 Session D68.2
            $0.00    0.008 Hrs File410
     $0.00  Estimated cost File410
     $0.00  Estimated cost this search
     $0.03  Estimated total session cost   0.010 Hrs.

SYSTEM:OS  - DIALOG OneSearch
  File   5:BIOSIS PREVIEWS(R)  1969-1998/Feb W2
         (c) 1998 BIOSIS
  File 155:MEDLINE(R)  1966-1998/Mar W4
         (c) format only 1998 The Dialog Corp
*File 155: reloaded for 1998
  File 357:Derwent Biotechnology Abs  1982-1998/Feb B2
         (c) 1998 Derwent Publ Ltd
  File 399:CA SEARCH(R)  1967-1998/UD=12806
         (c) 1998 American Chemical Society
*File 399: Use is subject to the terms of your user/customer agreement.
RANK charge added; see HELP RATES 399.
  File 351:DERWENT WPI  1963-1997/UD=9806;UP=9803;UM=9801
         (c)1998 Derwent Info Ltd
*File 351: Enter HELP NEWS 351 for info. about changes in DWPI coverage.
Output formats have changed for 1998.  Enter HELP FORM351 for details.
  File 653:US Pat.Fulltext  1980-1989
```

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        (c) format only 1998 Knight-Ridder Info
*File 653: Reassignment data now current through 08/28/97.
Reexamination, extension, expiration, reinstatement updated weekly.
  File 654:US PAT.FULL.  1990-1998/Feb 03
        (c) format only 1998 Knight-Ridder Info
*File 654: Reassignment data now current through 08/28/97.
Reexamination, extension, expiration, reinstatement updated weekly.

      Set  Items  Description
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? s telomerase and antisense

           1908  TELOMERASE
          29165  ANTISENSE
      S1    57  TELOMERASE AND ANTISENSE
? rd

>>>Duplicate detection is not supported for File 351.
>>>Duplicate detection is not supported for File 653.
>>>Duplicate detection is not supported for File 654.

>>>Records from unsupported files will be retained in the RD set.
...examined 50 records  (50)
...completed examining records
      S2    53  RD (unique items)
? s s2 and (RNA (w) component)

<------User Break------>
u!
? s s2 and (RNA (w) component or hTR)

Processing
              53  S2
          636298  RNA
         1115395  COMPONENT
             835  RNA(W)COMPONENT
            2494  HTR
      S3    21  S2 AND (RNA (W) COMPONENT OR HTR)
? s s2 and inhibit? and activity

Processing
              53  S2
         2359071  INHIBIT?
         2627474  ACTIVITY
      S4    31  S2 AND INHIBIT? AND ACTIVITY
? s s3 and s4

              21  S3
              31  S4
      S5    15  S3 AND S4
? t s5/7/all


 5/7/1     (Item 1 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs
(c) 1998 Derwent Publ Ltd. All rts. reserv.

218595  DBA Accession No.: 98-00192    PATENT
New peptide nucleic acids hybridizing specifically to mammalian
    telomerase RNA - antisense oligonucleotide analog for use
```

in therapy, and DNA probe for cancer diagnosis
AUTHOR: Shay J W; Wright W E; Piatyszek M A; Corey D; Norton J C
CORPORATE SOURCE: Menlo Park, CA, USA.
PATENT ASSIGNEE: Geron 1997
PATENT NUMBER: WO 9738013 PATENT DATE: 971016 WPI ACCESSION NO.: 97-512647 (9747)
PRIORITY APPLIC. NO.: US 630019 APPLIC. DATE: 960409
NATIONAL APPLIC. NO.: WO 97US5931 APPLIC. DATE: 970409
LANGUAGE: English
ABSTRACT: A new peptide nucleic acid (PNA) contains 6-25 nucleotides, which specifically hybridize to an **RNA component** of mammal **telomerase**, including GGG, which hybridizes to the template region. The PNA may have at least 1 N-terminal amine or amino acid, and a C-terminal amino acid or carboxylic acid. A protein (1-10,000 amino acids) which enhances cellular uptake of the PNA may be covalently linked to the PNA. The protein may contain the h-region of a signal peptide and the 3rd helix of Antp-HD. The PNA may be used to produce a liposome formulation for **inhibition** of mammal **telomerase activity**. The PNA may also be used as a DNA probe for detection of an **RNA component** of mammal **telomerase** in a sample, by hybridization, for diagnosis or prognosis of cancer, or for DNA fingerprinting in forensic applications (by detection of **telomerase** gene DNA polymorphisms). The PNA may be used in cancer therapy (generally as an **antisense** sequence). Since PNAs are uncharged, they hybridize rapidly to form thermodynamically stable duplexes with high resistance to protease and nuclease. (74pp)

5/7/2 (Item 2 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs

193162 DBA Accession No.: 96-03933 PATENT
RNA component of mammalian **telomerase**, especially human - useful or **antisense** oligonucleotide, ribozyme, and triple helix forming oligonucleotide production for use in therapy and transgenic mouse construction
AUTHOR: Villeponteau B; Feng J; Funk W; Andrews W H
CORPORATE SOURCE: Menlo Park, CA, USA.
PATENT ASSIGNEE: Geron 1996
PATENT NUMBER: WO 9601835 PATENT DATE: 960125 WPI ACCESSION NO.: 96-097581 (9610)
PRIORITY APPLIC. NO.: US 482115 APPLIC. DATE: 950607
NATIONAL APPLIC. NO.: WO 95US8530 APPLIC. DATE: 950706
LANGUAGE: English
ABSTRACT: The purified RNA (I) component of a mammalian **telomerase** (II) is claimed, where (I) has one of the disclosed RNA sequences. Also claimed are: a purified oligonucleotide (oligo) (**antisense** DNA, RNA, ribozyme or triple helix-forming oligo) comprising a sequence very similar or complementary to a contiguous sequence (10 to 500 nucleotides) of (I); the oligo which when bound to (I) **inhibits** or blocks the **activity** of (II); the oligo that is plasmid pGRN33 or a phage lambda clone 28-1; a recombinant plasmid containing the oligo and a promoter for use in oligo expression in cells; the plasmid containing a human gene for (I) (DNA sequence disclosed); a eukaryotic host cell containing the plasmid encoding RNA which associates with protein components of (II) to produce **telomerase activity** capable of adding sequences of repeating units of nucleotides to telomeres; production of recombinant (II) by culturing the transformed host; a composition of (I); identifying mutant mammalian (I);

inhibiting (II) **activity** in human cells by expression of **antisense** (II); a ribozyme; adeno virus carrying human (I); gene therapy; cancer diagnosis; DNA primers and DNA probes. (85pp)

5/7/3 (Item 1 from file: 351)
DIALOG(R)File 351:DERWENT WPI

011536166
WPI Acc No: 97-512647/199747
New peptide nucleic acids hybridising to mammalian **telomerase** RNA - used to **inhibit telomerase**, for treating tumours and other proliferative diseases, also for diagnosis
Patent Assignee: GERON CORP (GERO-N)
Inventor: COREY D; NORTON J C; PIATYSZEK M A; SHAY J W; WRIGHT W E
Number of Countries: 023 Number of Patents: 001
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Main IPC	Week
WO 9738013	A1	19971016	WO 97US5931	A	19970409	C07K-014/00	199747 B

Priority Applications (No Type Date): US 96630019 A 19960409
Cited Patents: 3.Jnl.Ref; WO 9714026
Patent Details:

Patent	Kind	Lan	Pg	Filing Notes	Application	Patent
WO 9738013	A1	E	76			

Designated States (National): AU CA CN JP KR MX
Designated States (Regional): AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE

Abstract (Basic): WO 9738013 A

New peptide nucleic acid (PNA; I), has a sequence of 6-25 nucleotides (nt) that hybridises specifically to an **RNA component** of mammalian **telomerase**, and includes GGG for specific hybridisation to the template region of this component.

USE - (I) are used: (i) to **inhibit telomerase activity** in mammalian, especially transformed human, cells, particularly for treatment of cancer (claimed) or (not claimed) other conditions associated with abnormal **telomerase activity** or metabolism, e.g. HIV infection, neurodegeneration, aging, and fungal infection, also as contraceptives, and (ii) to detect and quantify the **RNA component** of **telomerase** (by hybridisation) for diagnosis and prognosis of cancer. They can also be used forensically to identify individuals from polymorphism of the **telomerase** gene. (I) are generally **antisense** sequences but may also bind to a duplex, or are truncated/modified sense sequences that may act as competitive **inhibitors** of binding of **telomerase** to its holoenzyme. Sense sequences may also be used to activate **telomerase**, e.g. for treatment of AIDS, cardiac or cerebral disease, Alzheimer's disease, type I diabetes, for wound healing, etc. (not claimed).

ADVANTAGE - Since PNA are uncharged, they hybridise rapidly to form thermodynamically stable duplexes with high resistance to protease and nuclease.

Dwg.0/6

Derwent Class: B04; C06; D16
International Patent Class (Main): C07K-014/00
International Patent Class (Additional): A61K-038/16; C12Q-001/68

5/7/4 (Item 2 from file: 351)

DIALOG(R)File 351:DERWENT WPI

011122003
WPI Acc No: 97-099928/199709
DNA encoding essential RNA components of human **telomerase** - also truncated or recombinant **telomerase**, useful for diagnosis and treatment of cancer and infection by eukaryotic parasites
Patent Assignee: COLD SPRING HARBOR LAB (COLD-N)
Inventor: AUTEXIER C; GREIDER C
Number of Countries: 022 Number of Patents: 002
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Main IPC	Week
WO 9640868	A1	19961219	WO 96US9517	A	19960606	C12N-005/00	199709 B
AU 9661022	A	19961230	AU 9661022	A	19960606	C12N-005/00	199716

Priority Applications (No Type Date): US 95478352 A 19950607
Cited Patents: 3.Jnl.Ref; EP 666313; WO 9323572; WO 9513382
Patent Details:

Patent	Kind	Lan	Pg	Filing Notes	Application	Patent
WO 9640868	A1	E	48			

Designated States (National): AU CA JP MX US
Designated States (Regional): AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE

AU 9661022	A	Based on	WO 9640868

Abstract (Basic): WO 9640868 A

The following isolated sequences (I) of human **telomerase** (**hTR**) are new: (a) nucleotides (nt) 44-204; (b) nt 1-203, 1-273 or 1-418; (c) nt 44-204 and sequential deoxynucleotides but shorter than 1-445.

USE - The new RNA and DNA is used, in hybridisation assays, to detect or quantify **telomerase activity** in cells, tissue or fluid samples, e.g. for diagnosis of eukaryotic parasites (yeast and protozoa) or tumours. It is also useful as primers for amplification assays. The truncated or recombinant VT is used therapeutically to increase **telomerase activity** (also as reagents in the screening assay) while (II) or other **inhibitors** such as **antisense** molecules, are used to reduce such **activity**. Typical applications are initiation/restoration of **activity** to cause senescence or to prevent immortalisation of cells in tumours or parasites. (I) are also used to produce recombinant **telomerase**, which can then be used conventionally to raise antibodies for diagnostic detection of **telomerase**.

ADVANTAGE - Detecting **telomerase** allows early diagnosis of tumour or infection, before clinical signs are manifest. **Telomerase inhibitors** directed against e.g. Trypanosoma should cause fewer side effects than drugs currently used to treat such infections. (I) encodes those parts of **hTR** RNA essential for **activity** but are significantly shorter than the endogenous **RNA component**.

Dwg.0/7

Derwent Class: B04; C07; D16
International Patent Class (Main): C12N-005/00
International Patent Class (Additional): A61K-038/00; A61K-038/16; A61K-038/43; A61K-048/00; C07H-021/00; C12N-015/00; C12N-015/63; C12N-015/79

5/7/5 (Item 3 from file: 351)

DIALOG(R)File 351:DERWENT WPI

010600628
WPI Acc No: 96-097581/199610
RNA component of mammalian **telomerase**, esp. human - useful in identifying e.g. candidate **telomerase**-modulating agents
Patent Assignee: GERON CORP (GERO-N)
Inventor: ANDREWS W H; FENG J; FUNK W; VILLEPONTEAU B
Number of Countries: 065 Number of Patents: 007
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Main IPC	Week
WO 9601835	A1	19960125	WO 95US8530	A	19950706	C07H-021/00	199610 B
AU 9529647	A	19960209	AU 9529647	A	19950706	C07H-021/00	199619
NO 9700041	A	19970306	WO 95US8530	A	19950706	C07H-021/00	199721
			NO 9741	A	19970106		
FI 9700026	A	19970303	WO 95US8530	A	19950706	C12Q-000/00	199723
			FI 9726	A	19970103		
EP 778842	A1	19970618	EP 95925552	A	19950706	C07H-021/00	199729
			WO 95US8530	A	19950706		
CZ 9700034	A3	19971015	WO 95US8530	A	19950706	C12N-005/10	199748
			CZ 9734	A	19950706		
BR 9508254	A	19971223	BR 958254	A	19950706	C07H-021/00	199806
			WO 95US8530	A	19950706		

Priority Applications (No Type Date): US 95482115 A 19950607; US 94272102 A 19940707; US 94330123 A 19941027; US 95472802 A 19950607
Cited Patents: 05Jnl.Ref
Patent Details:

Patent	Kind	Lan	Pg	Filing Notes	Application	Patent
WO 9601835	A1	E	114			
Designated States (National): AM AT AU BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IS JP KE KG KP KR KZ LK LR LT LU LV MD MG MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TT UA UG US UZ VN						
Designated States (Regional): AT BE CH DE DK ES FR GB GR IE IT KE LU MC MW NL OA PT SD SE SZ UG						
AU 9529647	A			Based on		WO 9601835
EP 778842	A1	E		Based on		WO 9601835
Designated States (Regional): AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE						
CZ 9700034	A3			Based on		WO 9601835
BR 9508254	A			Based on		WO 9601835

Abstract (Basic): WO 9601835 A

An **RNA component** (I) of mammalian **telomerase** in substantially pure form is claimed.

USE - The RNA sequences, vectors and host cells are useful for the recombinant prodn. of an active **telomerase** mol. capable of adding sequences to telomeres of chromosomal DNA. Mutant mammalian **telomerase RNA component** polynucleotides can be identified by synthesising mutant sequences substantially identical to (I) and assaying for binding to **telomerase** protein. Also (I) can be used in identifying candidate **telomerase**-modulating agents. **Antisense** and triple-helix forming sequences can be used for **inhibiting telomerase activity** in cells, esp. neoplastic cells. Polynucleotides of 25 consecutive nucleotides identical or complementary to (I) linked to heterologous transcriptional regulatory sequences can be used for gene therapy of human disease. (I) can also be used for detecting the presence of a **telomerase**-related or neoplastic condition in a patient. The

primers and probes are used for determining the presence of mammalian **telomerase** RNA in a cell or cellular sample (all claimed).
Dwg.0/4
Derwent Class: B04; D16
International Patent Class (Main): C07H-021/00; C12N-005/10; C12Q-000/00
International Patent Class (Additional): C07H-021/02; C07H-021/04; C12N-009/12; C12N-015/11; C12N-015/52; C12N-015/63

5/7/6 (Item 1 from file: 654)
DIALOG(R)File 654:US PAT.FULL.

02735266
Utility
THERAPY AND DIAGNOSIS OF CONDITIONS RELATED TO TELOMERE LENGTH AND/OR **TELOMERASE ACTIVITY**

PATENT NO.: 5,707,795
ISSUED: January 13, 1998 (19980113)
INVENTOR(s): West, Michael D., Belmont, CA (California), US (United States of America)
Shay, Jerry, Dallas, TX (Texas), US (United States of America)
Wright, Woodring, Arlington, TX (Texas), US (United States of America)
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[Assignee Code(s): 83960]
APPL. NO.: 8-487,290
FILED: June 07, 1995 (19950607)
This application is a division of U.S. patent application Ser. No. 08-038,766, filed Mar. 24, 1993, now U.S. Pat. No. 5,489,508, issued Feb. 6, 1996, and which is a continuation-in-part of Michael D. West et al., entitled "**Telomerase Activity** Modulation and Telomere Diagnosis", filed May 13, 1992, and assigned U.S. Ser. No. 07-882,438 now abandoned, hereby incorporated by reference herein.

FULL TEXT: 2486 lines

ABSTRACT

Method and compositions are provided for the determination of telomere length and **telomerase activity**, as well as the ability to **inhibit telomerase activity** in the treatment of proliferative diseases. Particularly, primers are elongated under conditions which minimize interference from other genomic sequences, so as to obtain accurate determinations of telomeric length or **telomerase activity**. In addition, compositions are provided for intracellular **inhibition** of **telomerase activity**.

We claim:

1. A method for diagnosis of a stage of disease progression in an individual having a disease associated with an increased rate of proliferation of a cell population, said method comprising steps of:
(a) measuring telomere lengths of telomeres from a cell or tissue sample obtained from said individual to obtain a measured telomere length:
(b) comparing said measured telomere length to a control telomere length obtained by measuring telomere length ill a control sample; and

(c) correlating differences between said measured telomere length and said control telomere length with said stage of disease progression.

2. The method of claim 1, wherein said disease is HIV-infection or AIDS.

3. The method of claim 1, wherein said disease is atherosclerosis.

4. The method of claim 1, wherein said disease is cancer.

5. The method of claim 4, wherein said cancer is ovarian cancer.

6. The method of claim 4, wherein said cancer is breast cancer.

7. The method of claim 1, wherein said disease is Down's Syndrome.

8. The method of claim 1, wherein said disease is liver disease.

9. The method of claim 1, wherein said disease is muscular dystrophy.

10. The method of claim 1, wherein said measuring step comprises steps of:
(a) digesting genomic DNA of said sample to obtain terminal restriction fragments;
(b) separating said terminal restriction fragments by size;
(c) hybridizing an oligonucleotide probe complementary to telomeric DNA under conditions such that said probe hybridizes specifically to telomeric DNA in said terminal restriction fragments;
(d) measuring amount of bound probe; and
(e) correlating amount of bound probe with telomere length.

11. The method of claim 10, wherein said disease is HIV-infection or AIDS.

12. The method of claim 10, wherein said disease atherosclerosis.

13. The method of claim 10, wherein said disease is cancer.

14. The method of claim 10, wherein said condition is Down's Syndrome.

15. The method of claim 10, wherein said condition is liver disease.

16. The method of claim 10, wherein said condition is muscular dystrophy.

17. The method of claim 1, wherein said measuring step comprises steps of:
(a) adding a primer sufficiently complementary to a 3'-end of a telomere in double-stranded chromosomal DNA of said sample to hybridize specifically thereto in a mixture containing only those deoxynucleotides complementary to nucleotides in telomeric DNA under conditions such that said primer is extended by an agent for polymerization until reaching a non-telomeric deoxynucleotide to form a primer extension product complementary to telomeric DNA; and
(b) measuring primer extension product size to provide a measure of telomere length.

18. The method of claim 17, wherein said primer is 5'-CCCTAACCCTAACCCTAACCCTAA-3' (Seq. ID No. 6).

19. The method of claim 17, wherein one of said deoxynucleotides is radiolabeled.

20. The method of claim 17, wherein said disease is HIV-infection or AIDS.

21. The method of claim 17, wherein said disease atherosclerosis.

22. The method of claim 17, wherein said disease is cancer.

23. The method of claim 17, wherein said condition is Down's Syndrome.

24. The method of claim 17, wherein said condition is liver disease.

25. The method of claim 17, wherein said condition is muscular dystrophy.

26. The method of claim 1, wherein said measuring step comprises the steps of:
(a) denaturing cellular DNA of said sample in situ;
(b) adding an oligonucleotide probe labeled with a detectable label and complementary to telomeric DNA to said denatured DNA under conditions such that said probe anneals to said DNA;
(c) measuring signal intensity of said label from said probe annealed to said denatured DNA; and
(d) correlating said signal intensity with telomere length.

27. The method of claim 1, wherein said cell or tissue sample obtained from said individual is enriched for a particular cell type.

28. The method of claim 1, wherein said control sample is obtained from said individual at an earlier stage of disease progression.

29. The method of claim 1, wherein said stage of disease progression is a stage after the administration of a therapeutic for treating said disease.

30. The method of claim 2, wherein said disease is HIV-infection and said stage of disease progression is a stage after seroconversion and prior to AIDS.

31. The method of claim 2, wherein said sample obtained from said individual is a peripheral lymphocyte cell sample.

32. The method of claim 2, wherein said stage of disease progression is a stage after the administration of a therapeutic for treating said disease.

33. The method of claim 29, wherein said peripheral lymphocyte cell sample is a CD4 sup + cell sample.

5/7/7 (Item 2 from file: 654)
DIALOG(R)File 654:US PAT.FULL.

02724860

Utility
YEAST **TELOMERASE** COMPOSITIONS

PATENT NO.: 5,698,686
ISSUED: December 16, 1997 (19971216)
INVENTOR(s): Gottschling, Daniel E., Chicago, IL (Illinois), US (United States of America)
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ASSIGNEE(s): Arch Development Corporation, (A U.S. Company or Corporation), Chicago, IL (Illinois), US (United States of America)
[Assignee Code(s): 20681]
APPL. NO.: 8-431,080
FILED: April 28, 1995 (19950428)

The present invention is a continuation-in-part of U.S. patent application Ser. No. 08-326,781, filed Oct. 20, 1994, now abandoned, the entire text and figures of which disclosure is specifically incorporated herein by reference without disclaimer.

The U.S. Government owns rights in the present invention pursuant to National Institutes of Health Grants GM43893 and CA14599.

FULL TEXT: 7270 lines

ABSTRACT

Disclosed are various methods, compositions and screening assays connected with **telomerase**, including genes encoding the template RNA of S. cerevisiae **telomerase** and various **telomerase**-associated polypeptides.

What is claimed is:

1. A nucleic acid segment characterized as:
(a) an isolated nucleic acid segment comprising a sequence region that consists of at least 25 contiguous nucleotides that have the same sequence as, or are complementary to, 25 contiguous nucleotides of SEQ ID NO:1, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:19, SEQ ID NO:31 or SEQ ID NO:23; or (b) an isolated nucleic acid segment of from 25 to about 10,000 nucleotides in length that specifically hybridizes to the nucleic acid segment of SEQ ID NO:1, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:19, SEQ ID NO:31 or SEQ ID NO:23, or the complement thereof, under high stringency hybridization conditions.

2. The nucleic acid segment of claim 1, wherein the segment is characterized as comprising a sequence region of at least 25 contiguous nucleotides from SEQ ID NO:1, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:19, SEQ ID NO:31 or SEQ ID NO:23, or the complement thereof.

3. The nucleic acid segment of claim 1, wherein the segment is characterized as specifically hybridizing to the nucleic acid segment of SEQ ID NO:1, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:19, SEQ ID NO:31 or SEQ ID NO:23, or the complement thereof, under high stringency hybridization conditions.

4. The nucleic acid segment of claim 1, wherein the segment comprises a sequence region of at least 25 contiguous nucleotides from SEQ ID NO:1, or the complement thereof; or wherein the segment specifically hybridizes to the nucleic acid segment of SEQ ID NO:1, or the complement thereof, under high stringency hybridization conditions.

5. The nucleic acid segment of claim 1, wherein the segment comprises a sequence region of at least 25 contiguous nucleotides from SEQ ID NO:29, or the complement thereof; or wherein the segment specifically hybridizes to the nucleic acid segment of SEQ ID NO:29, or the complement thereof, under high stringency hybridization conditions.

6. The nucleic acid segment of claim 1, wherein the segment comprises a sequence region of at least 25 contiguous nucleotides from SEQ ID NO:30, or

the complement thereof; or wherein the segment specifically hybridizes to the nucleic acid segment of SEQ ID NO:30, or the complement thereof, under high stringency hybridization conditions.

7. The nucleic acid segment of claim 1, wherein the segment comprises a sequence region of at least 25 contiguous nucleotides from SEQ ID NO:19, or the complement thereof; or wherein the segment specifically hybridizes to the nucleic acid segment of SEQ ID NO:19, or the complement thereof, under high stringency hybridization conditions.

8. The nucleic acid segment of claim 1, wherein the segment comprises a sequence region of at least 25 contiguous nucleotides from SEQ ID NO:31, or the complement thereof; or wherein the segment specifically hybridizes to the nucleic acid segment of SEQ ID NO:31, or the complement thereof, under high stringency hybridization conditions.

9. The nucleic acid segment of claim 1, wherein the segment comprises a sequence region of at least 25 contiguous nucleotides from SEQ ID NO:23, or the complement thereof; or wherein the segment specifically hybridizes to the nucleic acid segment of SEQ ID NO:23, or the complement thereof, under high stringency hybridization conditions.

10. The nucleic acid segment of claim 1, wherein the segment comprises a sequence region of at least about 30 contiguous nucleotides; or wherein the segment that specifically hybridizes is about 30 nucleotides in length.

11. The nucleic acid segment of claim 10, wherein the segment comprises a sequence region of at least about 50 contiguous nucleotides; or wherein the segment that specifically hybridizes is about 50 nucleotides in length.

12. The nucleic acid segment of claim 11, wherein the segment comprises a sequence region of at least about 100 contiguous nucleotides; or wherein the segment that specifically hybridizes is about 100 nucleotides in length.

13. The nucleic acid segment of claim 12, wherein the segment comprises a sequence region of at least about 200 contiguous nucleotides; or wherein the segment that specifically hybridizes is about 200 nucleotides in length.

14. The nucleic acid segment of claim 13, wherein the segment comprises a sequence region of at least about 500 contiguous nucleotides; or wherein the segment that specifically hybridizes is about 500 nucleotides in length.

15. The nucleic acid segment of claim 14, wherein the segment comprises a sequence regxon that consists of the 1301 contiguous nucleotides of SEQ ID NO:1, or the complement thereof.

16. The nucleic acid segment of claim 14, wherein the segment comprises a sequence region that consists of at least a 1000 nucleotide long contiguous sequence from SEQ ID NO:29, or the complement thereof.

17. The nucleic acid segment of claim 16, wherein the segment comprises a sequence region that consists of the 1882 contiguous nucleotides of SEQ ID NO:29, or the complement thereof.

18. The nucleic acid segment of claim 14, wherein the segment comprises a sequence region that consists of the 1094 contiguous nucleotides of SEQ ID NO:30, or the complement thereof.

19. The nucleic acid segment of claim 14, wherein the segment comprises a sequence region that consists of at least a 1000 nucleotide long contiguous sequence from SEQ ID NO:19, or the complement thereof.

20. The nucleic acid segment of claim 19, wherein the segment comprises a sequence region that consists of at least a 2000 nucleotide long contiguous sequence from SEQ ID NO:19, or the complement thereof.

21. The nucleic acid segment of claim 20, wherein the segment comprises a sequence region that consists of the 2434 contiguous nucleotides of SEQ ID NO:19, or the complement thereof.

22. The nucleic acid segment of claim 14, wherein the segment comprises a sequence region that consists of the 807 contiguous nucleotides of SEQ ID NO:31, or the complement thereof.

23. The nucleic acid segment of claim 14, wherein the segment comprises a sequence region that consists of at least a 1000 nucleotide long contiguous sequence from SEQ ID NO:23, or the complement thereof.

24. The nucleic acid segment of claim 23, wherein the segment comprises a sequence region that consists of the 2117 contiguous nucleotides of SEQ ID NO:23, or the complement thereof.

25. The nucleic acid segment of claim 1, wherein the segment is up to 10,000 basepairs in length.

26. The nucleic acid segment of claim 25, wherein the segment is up to 5,000 basepairs in length.

27. The nucleic acid segment of claim 26, wherein the segment is up to 1,000 basepairs in length.

28. The nucleic acid segment of claim 27, wherein the segment is up to 500 basepairs in length.

29. The nucleic acid segment of claim 28, wherein the segment is up to 100 basepairs in length.

30. The nucleic acid segment of claim 1, further defined as a DNA segment.

31. The nucleic acid segment of claim 1, further defined as a RNA segment.

32. An isolated RNA segment of from 25 to about 1,500 nucleotides in length that comprises a non-ciliate **telomerase** RNA template, the RNA segment specifically hybridizing to the nucleic acid segment of SEQ ID NO:1 or the complement thereof under high stringency hybridization conditions.

33. The isolated RNA segment of claim 32, comprising a yeast **telomerase** RNA template.

34. An affinity column comprising a deoxyoligonucleotide attached to a solid support, wherein the deoxyoligonucleotide includes a GT-rich sequence complementary to the non-ciliate **telomerase** RNA template sequence from position 400 to position 500 of SEQ ID NO:1, and wherein the GT-rich sequence binds to a non-ciliate **telomerase** complex.

35. A DNA segment comprising an isolated gene that encodes a yeast

telomerase RNA template and includes a contiguous DNA sequence from position 400 to position 500 of SEQ ID NO:1.

36. The DNA segment of claim 35, comprising an isolated gene that includes a contiguous DNA sequence from position 200 to position 900 of SEQ ID NO:1.

37. The DNA segment of claim 35, comprising an isolated gene that includes the DNA sequence of SEQ ID NO:1.

38. A DNA segment comprising an isolated gene that encodes a polypeptide associated with yeast **telomerase**, wherein the polypeptide includes a contiguous amino acid sequence of at least about twelve amino acids from SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22 or SEQ ID NO:24.

39. The DNA segment of claim 38, comprising an isolated gene that encodes a polypeptide that includes a contiguous amino acid sequence from SEQ ID NO:16.

40. The DNA segment of claim 39, comprising an isolated gene that encodes a polypeptide having the sequence of SEQ ID NO:16.

41. The DNA segment of claim 40, comprising an isolated gene that includes the contiguous DNA sequence from position 54 to position 1799 of SEQ ID NO:29.

42. The DNA segment of claim 38, comprising an isolated gene that encodes a polypeptide that includes a contiguous amino acid sequence from SEQ ID NO:18.

43. The DNA segment of claim 42, comprising an isolated gene that encodes a polypeptide having the sequence of SEQ ID NO:18.

44. The DNA segment of claim 43, comprising an isolated gene that includes the contiguous DNA sequence from position 78 to position 1094 of SEQ ID NO:30.

45. The DNA segment of claim 38, comprising an isolated gene that encodes a polypeptide that includes a contiguous amino acid sequence from SEQ ID NO:20.

46. The DNA segment of claim 45, comprising an isolated gene that encodes a polypeptide having the sequence of SEQ ID NO:20.

47. The DNA segment of claim 46, comprising an isolated gene that includes the contiguous DNA sequence from position 2 to position 2368 of SEQ ID NO:19.

48. The DNA segment of claim 38, comprising an isolated gene that encodes a polypeptide that includes a contiguous amino acid sequence from SEQ ID NO:22.

49. The DNA segment of claim 48, comprising an isolated gene that encodes a polypeptide having the sequence of SEQ ID NO:22.

50. The DNA segment of claim 49, comprising an isolated gene that includes the contiguous DNA sequence from position 55 to position 699 of SEQ ID NO:31.

51. The DNA segment of claim 38, comprising an isolated gene that encodes

a polypeptide that includes a contiguous amino acid sequence from SEQ ID NO:24.

52. The DNA segment of claim 51, comprising an isolated gene that encodes a polypeptide having the sequence of SEQ ID NO:24.

53. The DNA segment of claim 52, comprising an isolated gene that includes the contiguous DNA sequence from position 3 to position 1955 of SEQ ID NO:23.

54. The DNA segment of claim 35 or 38, wherein the isolated gene is positioned under the control of a promoter.

55. The DNA segment of claim 54, positioned under the control of a recombinant promoter.

56. The DNA segment of claim 55, further defined as a recombinant vector.

57. A recombinant host cell incorporating a DNA segment in accordance with claim 41 or claim 45.

58. The recombinant host cell of claim 57, further defined as a prokaryotic host cell.

59. The recombinant host cell of claim 57, further defined as a eukaryotic host cell.

60. The recombinant host cell of claim 59, further defined as a yeast cell.

61. The recombinant host cell of claim 59, further defined as a mammalian cell.

62. The recombinant host cell of claim 57, wherein the host cell expresses the DNA segment to produce a **telomerase** RNA template or a polypeptide associated with **telomerase**.

63. The nucleic acid segment of claim 14, wherein the segment comprises a sequence region that consists of about a 1000 nucleotide long contiguous sequence from SEQ ID NO:29, or the complement thereof.

64. The nucleic acid segment of claim 14, wherein the segment comprises a sequence region that consists of about a 1000 nucleotide long contiguous sequence from SEQ ID NO:19, or the complement thereof.

65. The nucleic acid segment of claim 19, wherein the segment comprises a sequence region that consists of about a 2000 nucleotide long contiguous sequence from SEQ ID NO:19, or the complement thereof.

66. The nucleic acid segment of claim 14, wherein the segment comprises a sequence region that consists of about a 1000 nucleotide long contiguous sequence from SEQ ID NO:23, or the complement thereof.

67. The nucleic acid segment of claim 25, wherein the segment is about 10,000 basepairs in length.

68. The nucleic acid segment of claim 26, wherein the segment is about 5,000 basepairs in length.

69. The nucleic acid segment of claim 27, wherein the segment is about 1,000 basepairs in length.

70. The nucleic acid segment of claim 28, wherein the segment is about 500 basepairs in length.

71. The nucleic acid segment of claim 29, wherein the segment is about 100 basepairs in length.

5/7/8 (Item 3 from file: 654)
DIALOG(R)File 654:US PAT.FULL.

02721786

Utility

TELOMERASE ACTIVITY ASSAYS FOR DIAGNOSING PATHOGENIC INFECTIONS

PATENT NO.: 5,695,932
ISSUED: December 09, 1997 (19971209)
INVENTOR(s): West, Michael D., Belmont, CA (California), US (United States of America)
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ASSIGNEE(s): The Regents of the University of California, (A U.S. Company or Corporation), Oakland, CA (California), US (United States of America)
University of Texas System, (A U.S. Company or Corporation), Austin, TX (Texas), US (United States of America)
[Assignee Code(s): 13234; 83960]
APPL. NO.: 8-60,952
FILED: May 13, 1993 (19930513)
This application is a continuation-in-part of Michael D. West et al., entitled "Therapy and diagnosis of conditions related to telomere length and-or **telomerase activity**, filed Mar. 24, 1993, and assigned U.S. Ser. No. 08-038,766, U.S. Pat. No. 5,489,508 which is a continuation-in-part of Michael D. West et al., entitled "**Telomerase Activity** Modulation and Telomere Diagnosis", filed May 13, 1992, and assigned U.S. Ser. No. 07-882,438, abandoned both (including drawings) hereby incorporated by reference herein.

This invention was made with Government support under Grant No. GM-26259, awarded by the National Institute of Health. The Government has certain rights in this invention.

FULL TEXT: 4620 lines

ABSTRACT

Method and compositions are provided for the determination of telomere length and **telomerase activity**, as well as the ability to **inhibit telomerase activity** in the treatment of proliferative diseases. Particularly, primers are elongated under conditions which minimize interference from other genomic sequences, so as to obtain accurate determinations of telomeric length or **telomerase activity**. In addition, compositions are provided for intracellular

inhibition of **telomerase activity** and means are shown for slowing the loss of telomeric repeats in aging cells.
We claim:

1. A nucleic acid method for detecting the presence of a eukaryotic pathogen in a patient wherein presence of said eukaryotic pathogen is detected by their **telomerase activity** within a somatic cell population or tissue, comprising the steps of:
obtaining a sample of somatic tissue or cells from said patient;
determining whether **telomerase activity** is present within said sample in said patient; and
correlating presence of **telomerase activity** with presence of said eukaryotic pathogen.

2. A nucleic acid method for detecting the presence of a fungal infection in a patient wherein said fungal infection is detected by their **telomerase activity** within a somatic cell population or tissue, comprising the steps of:
obtaining a sample of somatic tissue or cells from said patient;
determining whether **telomerase activity** is present within said sample in said patient; and
correlating presence of **telomerase activity** with presence of said fungal infection.

3. The method of claim 2, wherein said method further comprises characterizing said fungal infection, by the steps of:
contacting said sample with an oligonucleotide probe complementary to a telomeric nucleic acid sequence of a fungal cell;
allowing said oligonucleotide probe to hybridize to telomeric nucleic acid of a fungal cell contained in said sample;
characterizing said fungal infection as a fungal infection by a particular genus or species of fungus, as measured by specific hybridization of said oligonucleotide probe.

4. The method of claim 3 wherein the fungal cell is of a genus selected from a group consisting of: Candida, Kluyveromyces, and Saccharomyces.

5. The method of claim 4 wherein the telomeric nucleic acid of the fungal cell comprises a sequence selected from the group consisting of:
ACGGATGTCTAAC (SEQ ID NO. 8);
TTCTTGGTGT (SEQ ID NO. 9);
ACGGATGTCACGA (SEQ ID NO. 10);
TCATTGGTGT (SEQ ID NO. 11);
AAGGATGTCACGA (SEQ ID NO. 12);
ACGGATGCAGACT (SEQ ID NO. 13);
CGCTTGGTGT (SEQ ID NO. 14);
ACGGATTTGATTAGTTATGTGGTGT (SEQ ID NO. 15);
ACGGATTTGATTAGGTATGTGGTGT (SEQ ID NO. 16);
CTGGGTGC (SEQ ID NO. 17);
TGTGGGGT (SEQ ID NO. 18);
GTGTAAGGATG (SEQ ID NO. 19); and,
T(G) sub 2-3 (TG) sub 1-6 (SEQ ID NOS. 20, and 47-57).

6. The method of claim 3 wherein the fungal cell is of a genus selected from a group consisting of: Sporothrix, Coccidioides, Histoplasma, Blastomyces, Paracoccidioides, Cryptococcus, Aspergillus, Mucor, and Rizopus.

7. A nucleic acid method for diagnosis of a malarial infection in a patient wherein said malarial infection is an infection by a malarium

selected from a group consisting of: Plasmodium vivax, Plasmodium ovale, Plasmodium malariae, and Plasmodium falciparum, wherein said method comprises the steps of:
obtaining a sample of somatic tissue or cells from said patient;
determining whether **telomerase activity** is present within said sample in said patient; and
correlating presence of **telomerase activity** with presence of said malarial infection.

8. The method of claim 1, wherein said determining whether **telomerase activity** is present comprises the steps of:
incubating said cells or tissue in a reaction mixture comprising an oligonucleotide primer that can serve as a substrate for **telomerase**-mediated primer extension, nucleoside triphosphates, and a buffer under conditions such that, if **telomerase activity** is present, said primer is extended by **telomerase**-mediated addition of nucleotides derived from said nucleoside triphosphates to said primer; and,
correlating extension of said primer with the presence of **telomerase** from a pathogen.

5/7/9 (Item 4 from file: 654)
DIALOG(R)File 654:US PAT.FULL.

02710965
Utility
METHODS FOR SCREENING FOR AGENTS WHICH MODULATE TELOMERE LENGTH

PATENT NO.: 5,686,245
ISSUED: November 11, 1997 (19971111)
INVENTOR(s): West, Michael D., Belmont, CA (California), US (United States of America)
Shay, Jerry, Dallas, TX (Texas), US (United States of America)
Wright, Woodring, Arlington, TX (Texas), US (United States of America)
ASSIGNEE(s): University of Texas System Board of Regents, (A U.S. Company or Corporation), Austin, TX (Texas), US (United States of America)
[Assignee Code(s):
APPL. NO.: 8-475,778
FILED: June 07, 1995 (19950607)
This is a division of application Ser. No. 08-038,766, now issued as U.S. Pat. No. 5,489,508, filed Mar. 24, 1993, hereby incorporated by reference herein in totality, including drawings, which is a continuation-in-part of Michael D. West et al., entitled "**Telomerase Activity** Modulation and Telomere Diagnosis", filed May 13, 1992, and assigned U.S. Ser. No. 07-882,438, now abandoned, hereby incorporated by reference herein.

FULL TEXT: 2429 lines

ABSTRACT

Method and compositions are provided for the determination of telomere length and **telomerase activity**, as well as the ability to **inhibit telomerase activity** in the treatment of proliferative diseases. Particularly, primers are elongated under conditions which minimize interference from other genomic sequences, so as to obtain accurate determinations of telomeric length or **telomerase**

activity. In addition, compositions are provided for intracellular **inhibition** of **telomerase activity**.

We claim:

1. A method for screening for agents which modulate telomere length, wherein said method comprises the steps of:
(a) contacting cells in vitro with an agent which potential modulates telomere length;
(b) measuring the length of telomeres in cells contacted with said agent and in cells not contacted with said agent, and
(c) correlating a difference in telomere length in cells contacted with said agent as compared to cells not contacted with said agent identification of an agent which modulates telomere length.

2. The method of claim 1, wherein said cells are human cells.

3. The method of claim 1, wherein said cells are immortal cells.

4. The method of claim 1, wherein the difference in telomere length of step (c) is that the length of telomeres in cells contacted with said agent is greater than the length of telomeres in cells not contacted with said agent.

5. The method of claim 1, wherein the difference in telomere length of step (c) is that the length of telomeres in cells contacted with said agent is less than the length of telomeres in cells not contacted with said agent.

6. The method of claim 1, wherein the measuring of step (b) comprises the steps of:
(a) digesting genomic DNA of said cells to obtain terminal restriction fragments;
(b) separating said terminal restriction fragments by size;
(c) hybridizing an oligonucleotide probe complementary to telomeric DNA under conditions such that said probe hybridizes specifically to telomeric DNA in said terminal restriction fragments;
(d) measuring amount of bound probe; and
(e) correlating mount of bound probe with telomere length.

7. The method of claim 1, wherein the measuring of step (b) comprises the steps of:
(a) adding a primer sufficiently complementary to a 3'-end of a telomere in double-stranded chromosomal DNA of said cells to hybridize specifically thereto under conditions such that said primer is extended by an agent for polymerization until reaching a non-telomeric deoxynucleotide to form a primer extension product complementary to telomeric DNA; and
(b) measuring primer extension product size to provide a measure of telomere length.

8. The method of claim 1, wherein the measuring of step (b) comprises the steps of:
(a) denaturing cellular DNA of said sample in situ;
(b) adding an oligonucleotide probe labeled with a detectable label and complementary to telomeric DNA to said denatured DNA under conditions such that said probe anneals to said DNA;
(c) measuring signal intensity of said label from said probe annealed to said denatured DNA; and
(d) correlating said signal intensity with telomere length.

9. The method of claim 1, wherein said cells are cancer cells.

5/7/10 (Item 5 from file: 654)
DIALOG(R)File 654:US PAT.FULL.

02668240
Utility
TELOMERASE DIAGNOSTIC METHODS

PATENT NO.: 5,648,215
ISSUED: July 15, 1997 (19970715)
INVENTOR(s): West, Michael D., San Carlos, CA (California), US (United States of America)
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ASSIGNEE(s): Board of Regents, The University of Texas System, (A U.S. Company or Corporation), Austin, TX (Texas), US (United States of America)
[Assignee Code(s): 83960]
APPL. NO.: 8-315,216
FILED: September 28, 1994 (19940928)

The present application is a continuation-in-part of U.S. patent application Ser. No. 08-255,774, filed Jun. 7, 1994, which is a continuation-in-part of Ser. Nos. 08-151,477 and 08-153,051, both of which were filed 12 Nov. 1993, which are continuations-in-part of Ser. No. 08-060,952, filed 13 May 1993, which is a continuation-in-part of Ser. No. 08-038,766, filed 24 Mar. 1993, which is a continuation-in-part of now abandoned Ser. No. 07-882,438, filed 13 May 1992. Each of the foregoing patent applications is incorporated herein by reference.

STATEMENT OF GOVERNMENT RIGHTS

A portion of the research and results described herein was supported by NIH grant Nos. AG07992 and CA50195, and the U.S. government may therefore have certain rights regarding the invention disclosed herein.

FULL TEXT: 1572 lines

ABSTRACT

The presence of **telomerase activity** in a human somatic tissue or cell sample is positively correlated with the presence of cancer and can be used to diagnose the course of disease progression in a patient.

We claim:

1. A method for detecting whether a human breast, prostate, colon, or lung tissue sample contains cancerous cells, said method comprising

(a) preparing a cell extract from said tissue sample;

(b) incubating an aliquot of said cell extract in a reaction mixture comprising a **telomerase** substrate and a buffer in which **telomerase** can catalyze the extension of said **telomerase** substrate;

(c) determining whether said **telomerase** substrate has been extended in step (b) by addition of telomeric repeat sequences; and

(d) correlating presence of cancerous cells in said sample with the addition of telomeric repeat sequences to said **telomerase** substrate

and absence of cancerous cells in said sample with no addition of telomeric repeat sequences to said **telomerase** substrate.

2. The method of claim 1, wherein said breast tissue sample is removed from tissue adjacent to a tumor.

3. The method of claim 1, wherein said breast tissue sample is removed from an individual previously diagnosed as having axillary node negative breast cancer.

4. The method of claim 1, wherein said prostate tissue sample is removed from tissue adjacent to a location at which cancer cells are known to have been present.

5. The method of claim 1, wherein said prostate tissue sample is removed from an individual previously diagnosed as having benign prostatic hyperplasia.

6. The method of claim 1, wherein said prostate tissue sample is removed from an individual previously diagnosed as having prostatic intraepithelial neoplasia.

7. The method of claim 1, wherein step (b) further comprises amplifying any extended **telomerase** substrates in said reaction mixture by an amplification method selected from the group consisting of polymerase chain reaction and ligation chain reaction.

8. A method for determining prognosis of a patient known to have cancer by detecting whether a tissue sample contains cancerous cells, said method comprising

(a) preparing a cell extract from said tissue sample;

(b) incubating an aliquot of said cell extract in a reaction mixture comprising a **telomerase** substrate and a buffer in which **telomerase** can catalyze the extension of said **telomerase** substrate;

(c) determining whether said **telomerase** substrate has been extended in step (b) by addition of telomeric repeat sequences;

(d) correlating presence of cancerous cells in said sample with the addition of telomeric repeat sequences to said **telomerase** substrate and absence of cancerous cells in said sample with no addition of telomeric repeat sequences to said **telomerase** substrate; and

(e) correlating a negative prognosis in said patient with a presence of cancerous cells in said sample, and a positive prognosis in said patient with an absence of cancerous cells in said patient.

9. The method of claim 8 wherein said tissue sample is an axillary-node breast tissue sample.

10. The method of claim 8 wherein said tissue sample is a prostate tissue sample.

11. The method of claim 10 wherein said prostate tissue sample is removed from a patient previously diagnosed as having prostatic intraepithelial neoplasia.

12. The method of claim 10 wherein said prostate tissue sample is removed from a patient previously diagnosed as having benign prostate hyperplasia.

02665738
Utility
THERAPY AND DIAGNOSIS OF CONDITIONS RELATED TO TELOMERE LENGTH AND/OR **TELOMERASE ACTIVITY**

PATENT NO.: 5,645,986
ISSUED: July 08, 1997 (19970708)
INVENTOR(s): West, Michael D., San Carlos, CA (California), US (United States of America)
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ASSIGNEE(s): Board of Reagents, The University of Texas System, (A U.S. Company or Corporation), Dallas, TX (Texas), US (United States of America)
Geron Corporation, (A U.S. Company or Corporation), Menlo Park , CA (California), US (United States of America)
The Reagents of the University of California, (A U.S. Company or Corporation), Oakland, CA (California), US (United States of America)
[Assignee Code(s): 13234; 37860; 83960]
APPL. NO.: 8-153,051
FILED: November 12, 1993 (19931112)
This application is a continuation-in-part of Michael D. West et al., entitled "Therapy and diagnosis of conditions related to telomere length and-or **telomerase activity** , filed May 13, 1993, and assigned U.S. Ser. No. 08-060,952 (hereby incorporated by reference herein), which is a continuation-in-part of Michael D. West et al., entitled "Therapy and diagnosis of conditions related to telomere length and-or **telomerase activity** ," filed Mar. 24, 1993, and assigned U.S. Ser. No. 08-038,766, now U.S. Pat. No. 5,489,508 which is a continuation-in-part of Michael D. West et al., entitled "**Telomerase Activity** Modulation and Telomere Diagnosis", filed May 13, 1992, and assigned U.S. Ser. No. 07-882,438, abandoned, all (including drawings) hereby incorporated by reference herein.

This invention was made with Government support under Grant No. GM-26259, awarded by the National Institute of Health. The Government has certain rights in this invention.

FULL TEXT: 5702 lines

ABSTRACT

Method and compositions are provided for the determination of telomere length and **telomerase activity** , as well as the ability to increase or decrease **telomerase activity** in the treatment of proliferative diseases. Particularly, primers are elongated under

conditions which minimize interference from other genomic sequences, so as to obtain accurate determinations of telomeric length or **telomerase activity**. In addition, compositions are provided for intracellular **inhibition** of **telomerase activity** and means are shown for slowing or reversing the loss of telomeric repeats in aging cells.

We claim:

1. Method for screening for an agent which **inhibits telomerase activity**, comprising the steps of

combining in a reaction mixture a potential said agent, an active **telomerase**, a substrate oligonucleotide for said **telomerase**, and nucleotide triphosphates;

incubating said reaction mixture for a predetermined time for said substrate oligonucleotide to be extended;

determining whether extended substrate oligonucleotide is formed by contacting products of said reaction mixture with an oligonucleotide probe which hybridizes to a telomere repeat sequence; and

comparing hybridization of said probe to said products with hybridization of said probe to products of a reaction mixture in which said agent is not present; and,

correlating reduced hybridization in presence of said agent compared with hybridization observed in absence of said agent with **inhibition** of **telomerase activity** by said agent.

2. Method of screening for an agent which **inhibits** human **telomerase** comprising the steps of: contacting human **telomerase** with a potential said agent in the presence of a biotin-labelled substrate oligonucleotide; incubating under conditions in which said **telomerase** will extend said oligonucleotide in the absence of said **inhibitor**; capturing any extended substrate oligonucleotide on an avidinylated solid support; contacting said oligonucleotide substrate with an oligonucleotide probe which hybridizes to a telomere repeat sequence; comparing hybridization of said probe to said oligonucleotide substrate with hybridization of said probe to products of a reaction mixture in which said agent is not present; and, correlating reduced hybridization in presence of said agent compared with hybridization observed in absence of said agent with **inhibition** of **telomerase activity** by said agent.

3. Method of claim 1 wherein said active **telomerase** is human **telomerase**.

4. Method of claim 1 wherein said active **telomerase** is fungal **telomerase**.

5. The method of claim 1 wherein said active **telomerase** is Tetrahymena **telomerase**.

6. The method of claim 1 wherein said method comprises immobilizing the products of the reaction mixture on a solid support.

7. The method of claim 1 wherein said test compound is an **inhibitor** of retrovital reverse transcriptase.

8. The method of claim 1 wherein said test compound is an oligonucleotide.

9. The method of claim 6 wherein said oligonucleotide template is labeled with a compound which facilitates binding of said oligonucleotide template to said solid support.

10. The method of claim 1 wherein said substrate oligonucleotide

comprises a telomere repeat sequence.

11. The method of claim 1 wherein said substrate oligonucleotide is a sequence 5' TTAGGGTTAGGGTTAGGG 3' (SEQ ID NO. 5).

12. The method of claim 1 wherein said substrate oligonucleotide is a sequence 5' GTTAGGGTTAGGGTTAGG 3' (SEQ ID NO. 31).

13. The method of claim 1 wherein said substrate oligonucleotide is a sequence 5' AATCCGTCGAGCAGAGTT 3' (SEQ ID NO. 32).

14. The method of claim 2 wherein said substrate oligonucleotide is a sequence 5' TTAGGGTTAGGGTTAGGG 3' (SEQ ID NO. 5).

15. The method of claim 2 wherein said substrate oligonucleotide is a sequence 5' GTTAGGGTTAGGGTTAGG 3' (SEQ ID NO. 31).

16. The method of claim 2 wherein said substrate oligonucleotide is a sequence 5' AATCCGTCGAGCAGAGTT 3' (SEQ ID NO. 32).

17. The method of claim 9 wherein said compound is biotin.

18. The method of claim 1 wherein said oligonucleotide probe is labeled with a radioisotope.

19. The method of claim 2 wherein said oligonucleotide probe is labeled with a radioisotope.

20. The method of claim 18 wherein said radioisotope is sup 32 P.

21. The method of claim 19 wherein said radioisotope is sup 32 P.

22. The method of claim 1 wherein said oligonucleotide probe is labeled with a fluorescent label.

23. The method of claim 1 wherein said oligonucleotide probe is labeled with an epitope for an antibody.

24. The method of claim 23 wherein said epitope is dioxygenin.

25. The method of claim 2 wherein said oligonucleotide probe is labeled with a fluorescent label.

26. The method of claim 2 wherein said oligonucleotide probe is labeled with an epitope for an antibody.

27. The method of claim 26 wherein said antibody is dioxygenin.

02663344

Utility

SYNTHETIC OLIGONUCLEOTIDES WHICH MIMIC TELOMERIC SEQUENCES FOR USE IN TREATMENT OF CANCER AND OTHER DISEASES

PATENT NO.: 5,643,890
ISSUED: July 01, 1997 (19970701)

INVENTOR(s): Iversen, Patrick L., Ralston, NE (Nebraska), US (United States of America)
Mata, John E., Omaha, NE (Nebraska), US (United States of America)
ASSIGNEE(s): The Board of Regents of the University of Nebraska, (A U.S. Company or Corporation), Lincoln, NE (Nebraska), US (United States of America)
[Assignee Code(s): 58949]
APPL. NO.: 8-381,097
FILED: January 31, 1995 (19950131)
FULL TEXT: 1075 lines

ABSTRACT

A method of **inhibiting** proliferation of immortal cells or cells that express **telomerase** is disclosed. The method includes introduction of synthetic oligonucleotides which mimic telomere motifs. Quite surprisingly applicant has demonstrated that a single telomere motif, TTAGGG exhibits greater cellular uptake and higher **inhibition** of proliferation than longer oligonucleotides, which were previously thought to be necessary to achieve sequence specific interaction with **telomerase**.

What is claimed is:

1. A method of **inhibiting** proliferation of and/or killing cells characterized by uncontrolled proliferation comprising:
contacting said cells with an oligonucleotide, said oligonucleotide having a nucleotide sequence consisting of a single human telomeric repeat motif.

2. The method of claim 1 wherein said cell is characterized by **telomerase activity**.

3. The method of claim 1 wherein said oligonucleotide is modified to resist enzyme degradation.

4. The method of claim 1 wherein said oligonucleotide has a phosphorothioate backbone modification.

5. The method of claim 1 wherein said cells are Burkitt's lymphoma or Chang cells.

6. The method of claim 1 wherein said oligonucleotide is a deoxyribonucleotide.

7. The method of claim 1 wherein said repeat is TTAGGG.

8. A method of **inhibiting** proliferation of and/or killing cells characterized by **telomerase** expression comprising:
contacting said cells with an oligonucleotide that **inhibits** expression of a sequence other than a telomere motif, said oligonucleotide comprising a sequence substantially analogous to a human telomere motif, wherein said oligonucleotide targets the C-myb gene.

9. The method of claim 8 wherein said telomere motif is selected from the group consisting of TGAGGG and TTCGGG.

10. The method of claim 8 wherein said oligonucleotide is a phosphorothioate oligonucleotide.

11. A method of **inhibiting** proliferation of cells which express **telomerase** comprising:
contacting said cells with an oligonucleotide which mimics a telomere motif, said oligonucleotide having a sequence selected from the group

consisting of TTAGGG (SEQ ID NO: 3), TAGGGT (SEQ ID NO: 7), AGGGTT (SEQ ID NO: 8), GGGTTA (SEQ ID NO: 9), GGTTAG (SEQ ID NO: 10), and GTTAGG (SEQ ID NO: 11).

12. The method of claim 11 wherein said oligonucleotide is modified to resist enzyme degradation.

13. The method of claim 11 wherein said oligonucleotide has a phosphorothioate backbone modification.

14. The method of claim 11 wherein said cells are Burkitt's lymphoma or Chang cells.

15. The method of claim 11 wherein said oligonucleotide is a deoxyribonucleotide.

16. The method of claim 11 wherein said repeat is TTAGGG.

17. The method of claim 11 wherein said oligonucleotide is a phosphorothioate oligonucleotide.

18. A pharmaceutical composition for **inhibiting** diseases characterized by uncontrolled proliferation of cells comprising:
a pharmaceutically effective amount of an oligonucleotide, said oligonucleotide having a sequence consisting of a single human telomere motif said motif selected from the group consisting of SEQ ID NOS: 3, 7, 8, 9, 10 and 11, and
a pharmaceutical carrier.

19. A method of **inhibiting** proliferation of and/or killing cells characterized by **telomerase activity** comprising:
contacting said cells with an oligonucleotide, said oligonucleotide having no more than one consecutive repeat sequence which mimics a human telomeric repeat motif.

20. The method of claim 19 wherein said oligonucleotide is modified to resist enzyme degradation.

21. The method of claim 19 wherein said oligonucleotide has a phosphorothioate backbone modification.

22. The method of claim 20 wherein said cells are Burkitt's lymphoma or Chang cells.

23. The method of claim 20 wherein said oligonucleotide is a deoxyribonucleotide.

24. The method of claim 20 wherein said repeat is TTAGGG.

25. A method of **inhibiting** proliferation of and/or killing cells characterized by **telomerase** expression comprising:
contacting said cells with an oligonucleotide that **inhibits** expression of a sequence other than a telomere motif, said oligonucleotide comprising a sequence substantially analagous to a human telomere motif, said sequence selected from the group consisting of TGAGGG and TTCGGG.

02598691

Utility

MAMMALIAN **TELOMERASE**

[Isolated, purified recombinant nucleic acid fragment comprising oligonucleotide having sequence complementary or identical to human genomic DNA sequence encoding **RNA component** of human **telomerase**]

PATENT NO.: 5,583,016
ISSUED: December 10, 1996 (19961210)
INVENTOR(s): Villeponteau, Bryant, San Carlos, CA (California), US (United States of America)
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ASSIGNEE(s): Geron Corporation, (A U.S. Company or Corporation), Menlo Park , CA (California), US (United States of America)
[Assignee Code(s): 37860]
APPL. NO.: 8-330,123
FILED: October 27, 1994 (19941027)

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. patent application Ser. No. 272,102 now abandoned filed 7 Jul. 1994, which is incorporated herein by reference.

FULL TEXT: 1679 lines

ABSTRACT

Nucleic acids comprising the **RNA component** of a mammalian **telomerase** are useful as pharmaceutical, therapeutic, and diagnostic reagents.

We claim:

1. An isolated and purified recombinant nucleic acid fragment comprising an oligonucleotide having a contiguous sequence of at least 25 nucleotides in a sequence complementary or identical to a human genomic DNA sequence encoding the **RNA component** of human **telomerase** located in an difference 2.5 kb HindIII-SacI insert of plasmid pGRN33 (ATCC 75926).

2. The isolated and purified recombinant nucleic acid of claim 1 that is an oligodeoxyribonucleotide.

3. The isolated and purified recombinant nucleic acid of claim 1 that is an oligoribonucleotide.

4. The isolated and purified recombinant nucleic acid of claim 1 that is complementary to the DNA encoding the **RNA component** of human **telomerase**.

5. The isolated and purified recombinant nucleic acid of claim 1 that is plasmid pGRN33 (ATCC 75926).

6. The isolated and purified recombinant nucleic acid of claim 1 that is lambda clone 28-1 (ATCC 75925).

7. The isolated and purified recombinant nucleic acid of claim 1 comprising the sequence: [See structure in original document]8## (SEQ ID NO: 3), wherein "T" also can be "U".

8. The isolated and purified recombinant nucleic acid of claim 1 comprising the sequence: [See structure in original document]9## (SEQ ID NO: 3) wherein "T" also can be "U".

9. The isolated and purified recombinant nucleic acid of claim 3 comprising the sequence: [See structure in original document]10## (SEQ ID NO: 1).

10. The isolated and purified recombinant nucleic acid of claim 1 further comprising a promoter positioned to drive transcription of an RNA complementary in sequence to said oligonucleotide.

11. The isolated and purified recombinant nucleic acid of claim 10 wherein the contiguous sequence is at least 50 nucleotides in length.

12. The isolated and purified recombinant nucleic acid of claim 10 wherein the contiguous sequence is at least 200 nucleotides in length.

13. The isolated and purified recombinant nucleic acid of claim 10 wherein the contiguous sequence is at least 400 nucleotides in length.

14. The isolated and purified recombinant nucleic acid of claim 10 wherein the contiguous sequence is at most 50 nucleotides in length.

15. The isolated and purified recombinant nucleic acid of claim 10 wherein said recombinant nucleic acid functions to produce the oligonucleotide in a prokaryotic host cell.

16. The isolated and purified recombinant nucleic acid of claim 10 wherein said recombinant nucleic acid functions to produce the oligonucleotide in a eukaryotic host cell.

17. The isolated and purified recombinant nucleic acid of claim 16 wherein said recombinant nucleic acid functions to produce the oligonucleotide in a human cell such that the RNA is capable of being assembled by the cell into a functional **telomerase** molecule.

18. The isolated and purified recombinant nucleic acid of claim 10 wherein the oligonucleotide comprises a human gene for the **RNA component** of human **telomerase**.

19. The isolated and purified recombinant nucleic acid of claim 10 comprising the sequence: [See structure in original document]11## (SEQ ID NO: 3), wherein "T" also can be "U".

20. The isolated and purified recombinant nucleic acid of claim 10 comprising the sequence: [See structure in original document]12## (SEQ ID NO: 3) wherein "T" also can be "U".

21. The isolated and purified recombinant nucleic acid of claim 1 comprising a promoter positioned to specifically drive the transcription of an RNA complementary in sequence to said oligonucleotide.

22. An isolated oligonucleotide between 25 and 1000 nucleotides in length in a sequence identical or complementary to a contiguous sequence contained within a human genomic DNA sequence "encoding the **RNA component** of human **telomerase** " located in an difference 2.5 kb HindIII-SacI

insert of plasmid pGRN33 (ATCC 75926).

23. The isolated oligonucleotide of claim 22 at most 200 nucleotides in length.

24. The isolated oligonucleotide of claim 22 at most 50 nucleotides in length.

25. The isolated oligonucleotide of claim 22 at least 50 nucleotides in length.

26. The isolated oligonucleotide of claim 25 at most 200 nucleotides in length.

27. The isolated oligonucleotide of claim 22 at least 200 nucleotides in length.

28. The isolated oligonucleotide of claim 22 at least 400 nucleotides in length.

29. The isolated oligonucleotide of any of claims 22-28 further comprising a label.

30. The isolated oligonucleotide of claim 29 wherein the label is a radioactive label, a fluorescent label, biotin or avidin.

31. Isolated **RNA component** of human **telomerase**.

32. An oligonucleotide of SEQ ID NO: 22, 23, 24 or 25.

33. A host cell transformed with a recombinant nucleic acid comprising an oligonucleotide having a contiguous sequence of at least 25 nucleotides in a sequence complementary or identical to a human genomic DNA sequence encoding the **RNA component** of human **telomerase** located in an difference 2.5 kb HindIII-Sac I insert of plasmid pGRN33 (ATCC 75926).

34. The host cell of claim 33 transformed with pGRN33 (ATCC 75926).

35. The host cell of claim 33 transformed with lambda clone 28-1 (ATCC 75925).

36. The host cell of claim 33 wherein the recombinant nucleic acid further comprises a promoter positioned to drive the transcription of an RNA having a sequence complementary to the oligonucleotide.

37. The host cell of claim 33 that is a eukaryotic cell.

38. The host cell of claim 37 wherein the recombinant nucleic acid encodes an RNA molecule that can associate with protein components of human **telomerase** to produce **telomerase activity** capable of adding sequences of repeating units of nucleotides to telomeres.

39. The host cell of claim 38, wherein said repeating unit is 5'-TTAGGG-3'.

40. The host cell of claim 38, wherein said repeating unit is not 5'-TTAGGG-3'.

41. The host cell of claim 37, wherein said RNA molecule comprises the sequence: [See structure in original document]13## (SEQ ID NO: 1).

42. The host cell of claim 37, wherein the recombinant nucleic acid comprises the sequence: [See structure in original document]14## (SEQ ID NO:3), wherein "T" also can be "U".

43. The host cell of claim 37, wherein the recombinant nucleic acid comprises the sequence: [See structure in original document]15## (SEQ ID NO: 3) wherein "T" also can be "U".

44. A method for producing the **RNA component** of human **telomerase** comprising the step of culturing a eukaryotic host cell transformed with a recombinant nucleic acid comprising a promoter positioned to drive the transcription of an oligonucleotide encoding an **RNA component** of human **telomerase**.

45. The method of claim 44 wherein the oligonucleotide encoding the **RNA component** of human **telomerase** includes a sequence from a human genomic DNA sequence located in an difference 2.5 kb HindIII-SacI insert of plasmid pGRN33 (ATCC 75926).

46. The method of claim 44 wherein the cell is a human cell.

47. A method for producing a recombinant **telomerase** enzyme, said method comprising transforming a eukaryotic host cell capable of expressing protein components of **telomerase** , with a recombinant nucleic acid comprising a promoter positioned to drive the transcription of an oligonucleotide encoding the **RNA component** of human **telomerase** , said recombinant nucleic acid functioning to produce the oligonucleotide in a eukaryotic cell, and culturing said host cells transformed with said vector under conditions such that the protein components and **RNA component** are expressed and assemble to form an active **telomerase** molecule capable of adding sequences to telomeres of chromosomal DNA.

48. The method of claim 47 wherein the RNA has a sequence identical to a contiguous sequence encoding the **RNA component** of human **telomerase** from a human genomic DNA sequence located in an difference 2.5 kb HindIII-SacI insert of plasmid pGRN33 (ATCC 75926).

49. The method of claim 48 wherein the cell is a human cell.

5/7/14 (Item 9 from file: 654)
DIALOG(R)File 654:US PAT.FULL.

02495931
Utility
THERAPY AND DIAGNOSIS OF CONDITIONS RELATED TO TELOMERE LENGTH AND/OR **TELOMERASE ACTIVITY**
[Detecting cancer in humans by determining whether oligonucleotide primer is extended when incubated with cell sample, nucleoside triphosphates, buffer]

PATENT NO.: 5,489,508
ISSUED: February 06, 1996 (19960206)
INVENTOR(s): West, Michael D., Belmont, CA (California), US (United States of America)
Shay, Jerry, Dallas, TX (Texas), US (United States of America)
Wright, Woodring, Arlington, TX (Texas), US (United States of

America)
ASSIGNEE(s): University of Texas System Board of Regents, (A U.S. Company or Corporation), Austin, TX (Texas), US (United States of America)
[Assignee Code(s): 83960]
APPL. NO.: 8-38,766
FILED: March 24, 1993 (19930324)
This application is a continuation-in-part of Michael D. West et al., entitled "**Telomerase Activity** Modulation and Telomere Diagnosis", filed May 13, 1992, and assigned U.S. Ser. No. 07-882,438, abandoned, hereby incorporated by reference herein.

FULL TEXT: 2370 lines

ABSTRACT

Method and compositions are provided for the determination of telomere length and **telomerase activity**, as well as the ability to **inhibit telomerase activity** in the treatment of proliferative diseases. Particularly, primers are elongated under conditions which minimize interference from other genomic sequences, so as to obtain accurate determinations of telomeric length or **telomerase activity**. In addition, compositions are provided for intracellular **inhibition** of **telomerase activity**.

We claim:

1. A method for detecting cancer in a human, said method comprising:
(a) obtaining a cell sample from said individual;
(b) lysing cells in said cell sample to form a cell lysate under conditions such that denaturation of **telomerase** does not occur;
(c) incubating an aliquot of said cell lysate in a reaction mixture comprising an oligonucleotide primer that can serve as a substrate for **telomerase**-mediated primer extension, nucleoside triphosphates, and a buffer under conditions such that, if **telomerase activity** is present, said primer is extended by **telomerase**-mediated addition of nucleotides derived from said nucleoside triphosphates to said primer;
(d) determining whether said primer has been extended; and
(e) correlating presence of an extended primer with presence of cancer cells in said human and absence of an extended primer with absence of cancer cells in said human.

2. The method of claim 1, wherein step (d) further comprises separating primers from other nucleic acids in said sample.

3. The method of claim 1, wherein said primer comprises a label that facilitates detection of extended primers or separation of primers from other nucleic acids in said sample.

4. The method of claim 1, wherein said nucleoside triphosphates are dATP, dTTP, and dGTP.

5. The method of claim 1, wherein said human has already been diagnosed as having a tumor, and said cell sample is obtained from a site at a margin of said tumor in said human.

6. The method of claim 1, wherein said human has already been diagnosed as having a tumor, and said cell sample is obtained from said tumor.

7. The method of claim 4, wherein one of said nucleoside triphosphates is labelled.

8. The method of claim 4, wherein said label is selected from the group of labels consisting of radiolabels, enzymes, and fluorescent labels.

9. The method of claim 8, wherein said label is sup 32 P.

10. The method of claim 9, wherein said nucleoside triphosphates are dATP, dTTP, and sup 32 P-dGTP.

11. The method of claim 10, wherein said primer is 5'-TTAGGGTTAGGGTTAGGG-3' (SEQ ID NO. 5).

5/7/15 (Item 10 from file: 654)
DIALOG(R)File 654:US PAT.FULL.

02470421

Utility

MODULATION OF PIF-1-TYPE HELICASES

[Identifying controllers of telomere formation or elongation]

PATENT NO.: 5,466,576
ISSUED: November 14, 1995 (19951114)
INVENTOR(s): Schulz, Vincent P., Seattle, WA (Washington), US (United States of America)
Zakian, Virginia A., Seattle, WA (Washington), US (United States of America)
ASSIGNEE(s): Fred Hutchinson Cancer Research Center, (A U.S. Company or Corporation), Seattle, WA (Washington), US (United States of America)
[Assignee Code(s): 14990]
APPL. NO.: 8-86,993
FILED: July 02, 1993 (19930702)

The invention described in this application may have had U.S. government support from National Institutes of Health grants GM-26938 and GM-43265. The U.S. government may have certain rights in the invention.

FULL TEXT: 1388 lines

ABSTRACT

Method for affecting viability of a eucaryotic cell by contacting the cell with a modulator of the **activity** of a PIF-1-type helicase in the cell. Such contacting specifically increases or decreases the specific **activity** of the helicase in the cell.

We claim:

1. A method for identifying a modulator of telomere formation or elongation, comprising the steps of:
contacting a potential modulator of telomere formation or elongation with a PIF-1-type helicase in the presence of cells, and assaying the **activity** of said PIF-1-type helicase in vitro or in vivo, wherein said modulator specifically increases or decreases said **activity** and thereby modulates said telomere formation or elongation.

2. The method of claim 1, wherein the PIF-1-type helicase affects telomere function but not mitochondrial function.

3. The method of claim 1, wherein telomere length or heterogeneity are assayed to determine the **activity** of said PIF-1-type helicase.

4. The method of claim 3, wherein **inhibition** of **activity** of said PIF-1-type helicase is determined by an increase in telomere length.

5. The method of claim 1, wherein loss of subtelomeric genes is monitored to determine the **activity** of said PIF-1-type helicase.

6. The method of claim 1, wherein altered specificity of telomere formation is monitored to determine the **activity** of said PIF-1-type helicase.

7. The method of claim 1, wherein increased de novo telomere formation on a broken chromosome is monitored to determine the **activity** of said PIF-1-type helicase.

8. A modulator of telomere formation or elongation which specifically increases or decreases the **activity** Of PIF-1-type helicase, said modulator identified by the method of claim 1 that is specific for telomere function and not mitochondrial function.

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? b 5, 155, 357, 399

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            $7.80    0.065 Hrs File654
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           $37.50  10 Types
    $45.30  Estimated cost File654
            OneSearch, 7 files,  0.133 Hrs FileOS
    $65.68  Estimated cost this search
    $65.71  Estimated total session cost   0.143 Hrs.

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  File 155:MEDLINE(R)  1966-1998/Mar W4
         (c) format only 1998 The Dialog Corp
*File 155: reloaded for 1998
  File 357:Derwent Biotechnology Abs  1982-1998/Feb B2
         (c) 1998 Derwent Publ Ltd
  File 399:CA SEARCH(R)  1967-1998/UD=12806
         (c) 1998 American Chemical Society
*File 399: Use is subject to the terms of your user/customer agreement.
RANK charge added; see HELP RATES 399.

      Set  Items  Description
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? s telomerase and antisense

           1841  TELOMERASE
          25179  ANTISENSE
      S1     31  TELOMERASE AND ANTISENSE
? s s1 and (RNA (w) component or hTR)

             31  S1
         618810  RNA
         308665  COMPONENT
            750  RNA(W)COMPONENT
           2129  HTR
      S2      8  S1 AND (RNA (W) COMPONENT OR HTR)
? s s2 and inhibit? and activity

              8  S2
        2037322  INHIBIT?
        2335983  ACTIVITY
      S3      3  S2 AND INHIBIT? AND ACTIVITY
? t s3/7/all


 3/7/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 1998 The Dialog Corp. All rts. reserv.

08713838   95381057
  The RNA component of human telomerase.
  Feng J; Funk WD; Wang SS; Weinrich SL; Avilion AA; Chiu CP; Adams RR;
Chang E; Allsopp RC; Yu J; et al
  Geron Corporation, Menlo Park, CA 94025, USA.
  Science (UNITED STATES) Sep 1 1995, 269 (5228) p1236-41, ISSN
0036-8075 Journal Code: UJ7
  Contract/Grant No.: AG09383, AG, NIA
  Languages: ENGLISH
  Document type: JOURNAL ARTICLE
  Eukaryotic chromosomes are capped with repetitive telomere sequences that
protect the ends from damage and rearrangements. Telomere repeats are
synthesized by telomerase, a ribonucleic acid (RNA)-protein complex.
Here, the cloning of the RNA component of human
telomerase, termed hTR, is described. The template region of
hTR encompasses 11 nucleotides (5'-CUAACCCUAAC) complementary to the
human telomere sequence (TTAGGG)n. Germline tissues and tumor cell lines
expressed more hTR than normal somatic cells and tissues, which have
no detectable telomerase activity . Human cell lines that
expressed hTR mutated in the template region generated the predicted
mutant telomerase activity. HeLa cells transfected with an
antisense hTR lost telomeric DNA and began to die after 23 to
26 doublings. Thus, human telomerase is a critical enzyme for the
long-term proliferation of immortal tumor cells.


 3/7/2     (Item 1 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs
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218595  DBA Accession No.: 98-00192    PATENT
New peptide nucleic acids hybridizing specifically to mammalian
    telomerase RNA - antisense oligonucleotide analog for use
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in therapy, and DNA probe for cancer diagnosis
AUTHOR: Shay J W; Wright W E; Piatyszek M A; Corey D; Norton J C
CORPORATE SOURCE: Menlo Park, CA, USA.
PATENT ASSIGNEE: Geron 1997
PATENT NUMBER: WO 9738013 PATENT DATE: 971016 WPI ACCESSION NO.: 97-512647 (9747)
PRIORITY APPLIC. NO.: US 630019 APPLIC. DATE: 960409
NATIONAL APPLIC. NO.: WO 97US5931 APPLIC. DATE: 970409
LANGUAGE: English
ABSTRACT: A new peptide nucleic acid (PNA) contains 6-25 nucleotides, which specifically hybridize to an **RNA component** of mammal **telomerase**, including GGG, which hybridizes to the template region. The PNA may have at least 1 N-terminal amine or amino acid, and a C-terminal amino acid or carboxylic acid. A protein (1-10,000 amino acids) which enhances cellular uptake of the PNA may be covalently linked to the PNA. The protein may contain the h-region of a signal peptide and the 3rd helix of Antp-HD. The PNA may be used to produce a liposome formulation for **inhibition** of mammal **telomerase activity**. The PNA may also be used as a DNA probe for detection of an **RNA component** of mammal **telomerase** in a sample, by hybridization, for diagnosis or prognosis of cancer, or for DNA fingerprinting in forensic applications (by detection of **telomerase** gene DNA polymorphisms). The PNA may be used in cancer therapy (generally as an **antisense** sequence). Since PNAs are uncharged, they hybridize rapidly to form thermodynamically stable duplexes with high resistance to protease and nuclease. (74pp)

3/7/3 (Item 2 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs

193162 DBA Accession No.: 96-03933 PATENT
RNA component of mammalian **telomerase**, especially human - useful or **antisense** oligonucleotide, ribozyme, and triple helix forming oligonucleotide production for use in therapy and transgenic mouse construction
AUTHOR: Villeponteau B; Feng J; Funk W; Andrews W H
CORPORATE SOURCE: Menlo Park, CA, USA.
PATENT ASSIGNEE: Geron 1996
PATENT NUMBER: WO 9601835 PATENT DATE: 960125 WPI ACCESSION NO.: 96-097581 (9610)
PRIORITY APPLIC. NO.: US 482115 APPLIC. DATE: 950607
NATIONAL APPLIC. NO.: WO 95US8530 APPLIC. DATE: 950706
LANGUAGE: English
ABSTRACT: The purified RNA (I) component of a mammalian **telomerase** (II) is claimed, where (I) has one of the disclosed RNA sequences. Also claimed are: a purified oligonucleotide (oligo) (**antisense** DNA, RNA, ribozyme or triple helix-forming oligo) comprising a sequence very similar or complementary to a contiguous sequence (10 to 500 nucleotides) of (I); the oligo which when bound to (I) **inhibits** or blocks the **activity** of (II); the oligo that is plasmid pGRN33 or a phage lambda clone 28-1; a recombinant plasmid containing the oligo and a promoter for use in oligo expression in cells; the plasmid containing a human gene for (I) (DNA sequence disclosed); a eukaryotic host cell containing the plasmid encoding RNA which associates with protein components of (II) to produce **telomerase activity** capable of adding sequences of repeating units of nucleotides to telomeres; production of recombinant (II) by culturing the transformed host; a composition of (I); identifying mutant mammalian (I);

inhibiting (II) **activity** in human cells by expression of **antisense** (II); a ribozyme; adeno virus carrying human (I); gene therapy; cancer diagnosis; DNA primers and DNA probes. (85pp)

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? logoff

       10feb98 17:25:58 User233835 Session D68.4
            $0.90    0.015 Hrs File5
     $0.90  Estimated cost File5
            $0.33    0.011 Hrs File155
               $0.20  1 Type(s) in Format  7
            $0.20  1 Types
     $0.53  Estimated cost File155
            $0.41    0.003 Hrs File357
               $4.00  2 Type(s) in Format  7
            $4.00  2 Types
     $4.41  Estimated cost File357
            $2.40    0.020 Hrs File399
     $2.40  Estimated cost File399
            OneSearch, 4 files,  0.050 Hrs FileOS
     $8.24  Estimated cost this search
    $73.95  Estimated total session cost   0.193 Hrs.
Logoff: level 98.01.01 D  17:25:58


Trying 9158046...Open


box200> enter system id

Logging in to Dialog



DIALOG INFORMATION SERVICES
PLEASE LOGON:
 ********
IALOG Invalid account number

DIALOG INFORMATION SERVICES
PLEASE LOGON:
 ********
ENTER PASSWORD:
 t840lcpq
 ********
Welcome to DIALOG

Dialog level 98.01.01D

Last logoff:  14feb98 19:19:36
Logon file001 16feb98 13:00:18
ANNOUNCEMENT   ****    ANNOUNCEMENT   ****    ANNOUNCEMENT
NEW
***TableBase (File 93)
***U.S. Newswire (File 605)
***OneSearch REPORT TITLES available in Market Research Files
***DIALOG Direct(SM) Launched!
                          ***
RELOADS
***Derwent Patent Citation Index, File 342, now updating
***Medline, Files 154,155
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***BioCommerce Abstracts and Directory, File 286
***IMSWorld Patents International, Files 447 and 947
***CLAIMS/U.S. PATENTS (File 340): The complete patent collection
   is now in a single file (Dialog File 340) which incorporates
   the following discontinued CLAIMS files: 125,23,24,25. Updates
   are now weekly.
***CLAIMS/UNITERM (File 341) now incorporates the following
   discontinued CLAIMS files: 223,224,225.
***CLAIMS/COMPREHESIVE (File 942) now incorporates the following
   discontinued files: 923,924,925.
                          ***
FORMAT CHANGES
***Derwent World Patents Index (Files 351/352) display
   formats have changed. See HELP NEWS351.
                          ***
REMOVED
***American Statistics Index, File 102, Removed February 1
                          ***
DIALOG ONDISC(TM)
***New Dialog OnDisc(TM):  British Education Index
                          ***
UPDATE '98
***Early bird registration discount extended. Register before
   January 31 and pay only $199. April 15-17 in Philadelphia.
                          ***
PRICE CHANGES
***Prices have been adjusted in a number of Dialog databases
   as of January 1. Updated price list is available via
   ASAF (document numbers 5008-5011) and on the Web at
   http://phoenix.dialog.com/products/dialog/dial_pricing.html.

     >>> Enter BEGIN HOMEBASE for Dialog Announcements <<<
     >>>    of new databases, price changes, etc.      <<<
     >>>    Announcements last updated    2Feb98       <<<
* * * New CURRENT year ranges installed.* * *

* * * File 480 is temporarily unavailable. * * *

File   1:ERIC  1966-1997/Dec
       (c) format only 1998 The Dialog Corporation

      Set  Items  Description
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? b 410

       16feb98 13:00:24 User233835 Session D75.1
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     $0.03  Estimated cost File1
     $0.03  Estimated cost this search
     $0.03  Estimated total session cost   0.001 Hrs.

File 410:Chronolog(R)  1981-1998/Jan
       (c) 1998 The Dialog Corporation plc

      Set  Items  Description
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? set hi ;set hi

HILIGHT set on as ''
HILIGHT set on as ''
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? b 5, 155, 357, 399, 351

       16feb98 13:00:48 User233835 Session D75.2
            $0.00    0.006 Hrs File410
     $0.00  Estimated cost File410
     $0.00  Estimated cost this search
     $0.03  Estimated total session cost   0.008 Hrs.

SYSTEM:OS  - DIALOG OneSearch
  File   5:BIOSIS PREVIEWS(R)  1969-1998/Feb W2
         (c) 1998 BIOSIS
  File 155:MEDLINE(R)  1966-1998/Apr W1
         (c) format only 1998 Dialog Corporation
*File 155: Due to technical problems, 1998 MEDLINE has been
           restored to the 1997 version.
  File 357:Derwent Biotechnology Abs  1982-1998/Feb B2
         (c) 1998 Derwent Publ Ltd
  File 399:CA SEARCH(R)  1967-1998/UD=12807
         (c) 1998 American Chemical Society
*File 399: Use is subject to the terms of your user/customer agreement.
RANK charge added; see HELP RATES 399.
  File 351:DERWENT WPI  1963-1997/UD=9807;UP=9804;UM=9802
         (c)1998 Derwent Info Ltd
*File 351: Enter HELP NEWS 351 for info. about changes in DWPI coverage.
Output formats have changed for 1998.  Enter HELP FORM351 for details.

      Set  Items  Description
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? b 5, 155, 357, 399, 351, 654

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            $0.06    0.001 Hrs File5
     $0.06  Estimated cost File5
            $0.03    0.001 Hrs File155
     $0.03  Estimated cost File155
            $0.14    0.001 Hrs File357
     $0.14  Estimated cost File357
            $0.12    0.001 Hrs File399
     $0.12  Estimated cost File399
            $0.22    0.001 Hrs File351
     $0.22  Estimated cost File351
            OneSearch, 5 files,  0.009 Hrs FileOS
     $0.57  Estimated cost this search
     $0.60  Estimated total session cost   0.018 Hrs.

SYSTEM:OS  - DIALOG OneSearch
  File   5:BIOSIS PREVIEWS(R)  1969-1998/Feb W2
         (c) 1998 BIOSIS
  File 155:MEDLINE(R)  1966-1998/Apr W1
         (c) format only 1998 Dialog Corporation
*File 155: Due to technical problems, 1998 MEDLINE has been
           restored to the 1997 version.
  File 357:Derwent Biotechnology Abs  1982-1998/Feb B2
         (c) 1998 Derwent Publ Ltd
  File 399:CA SEARCH(R)  1967-1998/UD=12807
         (c) 1998 American Chemical Society
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RANK charge added; see HELP RATES 399.
  File 351:DERWENT WPI  1963-1997/UD=9807;UP=9804;UM=9802
         (c)1998 Derwent Info Ltd
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*File 351: Enter HELP NEWS 351 for info. about changes in DWPI coverage.
Output formats have changed for 1998. Enter HELP FORM351 for details.
File 654:US PAT.FULL. 1990-1998/Feb 10
(c) format only 1998 Knight-Ridder Info
*File 654: Reassignment data now current through 08/28/97.
Reexamination, extension, expiration, reinstatement updated weekly.

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      Set  Items  Description
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? s telomerase and (RNA or ribonucleoprotein)

           1936  TELOMERASE
         637397  RNA
          12067  RIBONUCLEOPROTEIN
      S1    583  TELOMERASE AND (RNA OR RIBONUCLEOPROTEIN)
? s s1 and RNAse H

            583  S1
              0  RNASE H
      S2      0  S1 AND RNASE H
? s s1 and oligo(w)decoration

            583  S1
         141365  OLIGO
          14263  DECORATION
              0  OLIGO(W)DECORATION
      S3      0  S1 AND OLIGO(W)DECORATION
? s s1 and accessible

            583  S1
          87676  ACCESSIBLE
      S4     13  S1 AND ACCESSIBLE
? rd

>>>Duplicate detection is not supported for File 351.
>>>Duplicate detection is not supported for File 654.

>>>Records from unsupported files will be retained in the RD set.
...completed examining records
      S5     11  RD (unique items)
? t s5/7/all


 5/7/1     (Item 1 from file: 5)
DIALOG(R)File   5:BIOSIS PREVIEWS(R)
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13798797     BIOSIS Number: 99798797
  Identification of determinants for inhibitor binding within the RNA
active site of human telomerase using PNA scanning
  Hamilton S E; Pitts A E; Katipaly R R; Jia X; Rutter J P; Davies B A;
Shay J W; Wright W E; Corey D R
  Dep. Pharmacol. Biochem., Howard Hughes Med. Inst., 5323 Harry Hines
Boulevard, Dallas, TX 75235, USA
  Biochemistry 36 (39). 1997. 11873-11880.
  Full Journal Title: Biochemistry
  ISSN: 0006-2960
  Language: ENGLISH
  Print Number: Biological Abstracts Vol. 104 Iss. 011 Ref. 156401
  Telomerase is a ribonucleoprotein that participates in the
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maintenance of telomere length. Its activity is up-regulated in many tumor types, suggesting that it may be a novel target for chemotherapy. The **RNA** component of **telomerase** contains an active site that plays at least two roles-binding telomere ends and templating their replication (Greider, C. W., & Blackburn, E. H. (1989) Nature 337, 331-337). The accessibility of **RNA** nucleotides for inhibitor binding cannot be assumed because of the potential for **RNA** secondary structure and **RNA** -protein interactions. Here we use high-affinity recognition by overlapping peptide nucleic acids (PNAs) (Nielsen, P. E., et al. (1991) Science 254, 1497- 1500) to identify nucleotides within the **RNA** active site of **telomerase** that are determinants for inhibitor recognition. The IC-50 for inhibition decreases from 30 mu-M to 10 nM as cytidines 50-52 (C50-52) at the boundary between the alignment and elongation domains are recognized by PNAs overlapping from the 5' direction. As C50-52 are uncovered in the 3' direction, IC-50 increases from 10 nM to 300 nM. As cytidine 56 at the extreme 3' end of the active site is uncovered, IC-50 values increase from 0.5 mu-M to 10 mu-M. This analysis demonstrates that C50-C52 and C56 are important for PNA recognition and are physically **accessible** for inhibitor binding. We use identification of these key determinants to minimize the size of PNA inhibitors, and knowledge of these determinants should facilitate design of other small molecules capable of targeting **telomerase**. The striking differences in IC-50 values for inhibition of **telomerase** activity by related PNAs emphasize the potential of PNAs to be sensitive probes for mapping complex nucleic acids. We also find that PNA hybridization is sensitive to nearest-neighbor interactions, and that consecutive guanine bases within a PNA strand increase binding to complementary DNA and **RNA** sequences.

5/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

10939560 BIOSIS Number: 97139560
DNA bound by the Oxytricha telomere protein is **accessible** to **telomerase** and other DNA polymerases
Shippen D E; Blackburn E H; Price C M
Dep. Chem., Univ. Nebr., Lincoln, NB 68588, USA
Proceedings of the National Academy of Sciences of the United States of America 91 (1). 1994. 405-409.
Full Journal Title: Proceedings of the National Academy of Sciences of the United States of America
ISSN: 0027-8424
Language: ENGLISH
Print Number: Biological Abstracts Vol. 097 Iss. 007 Ref. 089438
Macronuclear telomeres in Oxytricha exist as DNA-protein complexes in which the termini of the G-rich strands are bound by a 97-kDa telomere protein. During telomeric DNA replication, the replication machinery must have access to the G-rich strand. However, given the stability of telomere protein binding, it has been unclear how this is accomplished. In this study we investigated the ability of several different DNA polymerases to access telomeric DNA in Oxytricha telomere protein-DNA complexes. Although DNA bound by the telomere protein is not degraded by micrococcal nuclease or labeled by terminal deoxynucleotidyltransferase, this DNA serves as an efficient primer for the addition of telomeric repeats by **telomerase**, a specialized **RNA**-dependent DNA polymerase (**ribonucleoprotein** reverse transcriptase), EC 2.7.7.49. Moreover, in the presence of a suitable complementary C-rich DNA template, AMV reverse transcriptase and the E. coli Klenow fragment will also elongate DNA bound by the telomere

protein. These findings indicate that the 3' terminus and the Watson-Crick base pairing positions are exposed in the protein complex. We propose that the telomere protein can serve a dual role at the telomere by protecting the DNA phosphate backbone from degradation while simultaneously exposing the DNA bases for replication.

5/7/3 (Item 1 from file: 654)
DIALOG(R)File 654:US PAT.FULL.

02735266

Utility
THERAPY AND DIAGNOSIS OF CONDITIONS RELATED TO TELOMERE LENGTH AND/OR **TELOMERASE** ACTIVITY

PATENT NO.: 5,707,795
ISSUED: January 13, 1998 (19980113)
INVENTOR(s): West, Michael D., Belmont, CA (California), US (United States of America)
Shay, Jerry, Dallas, TX (Texas), US (United States of America)
Wright, Woodring, Arlington, TX (Texas), US (United States of America)
ASSIGNEE(s): Board of Regents, The University of Texas System, (A U.S. Company or Corporation), Austin, TX (Texas), US (United States of America)
[Assignee Code(s): 83960]
APPL. NO.: 8-487,290
FILED: June 07, 1995 (19950607)
This application is a division of U.S. patent application Ser. No. 08-038,766, filed Mar. 24, 1993, now U.S. Pat. No. 5,489,508, issued Feb. 6, 1996, and which is a continuation-in-part of Michael D. West et al., entitled "**Telomerase** Activity Modulation and Telomere Diagnosis", filed May 13, 1992, and assigned U.S. Ser. No. 07-882,438 now abandoned, hereby incorporated by reference herein.

FULL TEXT: 2486 lines

ABSTRACT

Method and compositions are provided for the determination of telomere length and **telomerase** activity, as well as the ability to inhibit **telomerase** activity in the treatment of proliferative diseases. Particularly, primers are elongated under conditions which minimize interference from other genomic sequences, so as to obtain accurate determinations of telomeric length or **telomerase** activity. In addition, compositions are provided for intracellular inhibition of **telomerase** activity.

We claim:

1. A method for diagnosis of a stage of disease progression in an individual having a disease associated with an increased rate of proliferation of a cell population, said method comprising steps of:
(a) measuring telomere lengths of telomeres from a cell or tissue sample obtained from said individual to obtain a measured telomere length:
(b) comparing said measured telomere length to a control telomere length obtained by measuring telomere length ill a control sample; and
(c) correlating differences between said measured telomere length and said control telomere length with said stage of disease progression.

2. The method of claim 1, wherein said disease is HIV-infection or AIDS.

3. The method of claim 1, wherein said disease is atherosclerosis.

4. The method of claim 1, wherein said disease is cancer.

5. The method of claim 4, wherein said cancer is ovarian cancer.

6. The method of claim 4, wherein said cancer is breast cancer.

7. The method of claim 1, wherein said disease is Down's Syndrome.

8. The method of claim 1, wherein said disease is liver disease.

9. The method of claim 1, wherein said disease is muscular dystrophy.

10. The method of claim 1, wherein said measuring step comprises steps of:
(a) digesting genomic DNA of said sample to obtain terminal restriction fragments;
(b) separating said terminal restriction fragments by size;
(c) hybridizing an oligonucleotide probe complementary to telomeric DNA under conditions such that said probe hybridizes specifically to telomeric DNA in said terminal restriction fragments;
(d) measuring amount of bound probe; and
(e) correlating amount of bound probe with telomere length.

11. The method of claim 10, wherein said disease is HIV-infection or AIDS.

12. The method of claim 10, wherein said disease atherosclerosis.

13. The method of claim 10, wherein said disease is cancer.

14. The method of claim 10, wherein said condition is Down's Syndrome.

15. The method of claim 10, wherein said condition is liver disease.

16. The method of claim 10, wherein said condition is muscular dystrophy.

17. The method of claim 1, wherein said measuring step comprises steps of:
(a) adding a primer sufficiently complementary to a 3'-end of a telomere in double-stranded chromosomal DNA of said sample to hybridize specifically thereto in a mixture containing only those deoxynucleotides complementary to nucleotides in telomeric DNA under conditions such that said primer is extended by an agent for polymerization until reaching a non-telomeric deoxynucleotide to form a primer extension product complementary to telomeric DNA; and
(b) measuring primer extension product size to provide a measure of telomere length.

18. The method of claim 17, wherein said primer is 5'-CCCTAACCCTAACCCTAACCCTAA-3' (Seq. ID No. 6).

19. The method of claim 17, wherein one of said deoxynucleotides is radiolabeled.

20. The method of claim 17, wherein said disease is HIV-infection or

AIDS.

21. The method of claim 17, wherein said disease atherosclerosis.

22. The method of claim 17, wherein said disease is cancer.

23. The method of claim 17, wherein said condition is Down's Syndrome.

24. The method of claim 17, wherein said condition is liver disease.

25. The method of claim 17, wherein said condition is muscular dystrophy.

26. The method of claim 1, wherein said measuring step comprises the steps of:
(a) denaturing cellular DNA of said sample in situ;
(b) adding an oligonucleotide probe labeled with a detectable label and complementary to telomeric DNA to said denatured DNA under conditions such that said probe anneals to said DNA;
(c) measuring signal intensity of said label from said probe annealed to said denatured DNA; and
(d) correlating said signal intensity with telomere length.

27. The method of claim 1, wherein said cell or tissue sample obtained from said individual is enriched for a particular cell type.

28. The method of claim 1, wherein said control sample is obtained from said individual at an earlier stage of disease progression.

29. The method of claim 1, wherein said stage of disease progression is a stage after the administration of a therapeutic for treating said disease.

30. The method of claim 2, wherein said disease is HIV-infection and said stage of disease progression is a stage after seroconversion and prior to AIDS.

31. The method of claim 2, wherein said sample obtained from said individual is a peripheral lymphocyte cell sample.

32. The method of claim 2, wherein said stage of disease progression is a stage after the administration of a therapeutic for treating said disease.

33. The method of claim 29, wherein said peripheral lymphocyte cell sample is a CD4 sup + cell sample.

5/7/4 (Item 2 from file: 654)
DIALOG(R)File 654:US PAT.FULL.

02724860
Utility
YEAST **TELOMERASE** COMPOSITIONS

PATENT NO.: 5,698,686
ISSUED: December 16, 1997 (19971216)
INVENTOR(s): Gottschling, Daniel E., Chicago, IL (Illinois), US (United States of America)
Singer, Miriam S., Chicago, IL (Illinois), US (United States of America)
ASSIGNEE(s): Arch Development Corporation, (A U.S. Company or Corporation), Chicago, IL (Illinois), US (United States of America)

[Assignee Code(s): 20681]
APPL. NO.: 8-431,080
FILED: April 28, 1995 (19950428)

The present invention is a continuation-in-part of U.S. patent application Ser. No. 08-326,781, filed Oct. 20, 1994, now abandoned, the entire text and figures of which disclosure is specifically incorporated herein by reference without disclaimer.

The U.S. Government owns rights in the present invention pursuant to National Institutes of Health Grants GM43893 and CA14599.

FULL TEXT: 7270 lines

ABSTRACT

Disclosed are various methods, compositions and screening assays connected with **telomerase**, including genes encoding the template **RNA** of S. cerevisiae **telomerase** and various **telomerase**-associated polypeptides.

What is claimed is:

1. A nucleic acid segment characterized as:
(a) an isolated nucleic acid segment comprising a sequence region that consists of at least 25 contiguous nucleotides that have the same sequence as, or are complementary to, 25 contiguous nucleotides of SEQ ID NO:1, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:19, SEQ ID NO:31 or SEQ ID NO:23; or (b) an isolated nucleic acid segment of from 25 to about 10,000 nucleotides in length that specifically hybridizes to the nucleic acid segment of SEQ ID NO:1, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:19, SEQ ID NO:31 or SEQ ID NO:23, or the complement thereof, under high stringency hybridization conditions.

2. The nucleic acid segment of claim 1, wherein the segment is characterized as comprising a sequence region of at least 25 contiguous nucleotides from SEQ ID NO:1, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:19, SEQ ID NO:31 or SEQ ID NO:23, or the complement thereof.

3. The nucleic acid segment of claim 1, wherein the segment is characterized as specifically hybridizing to the nucleic acid segment of SEQ ID NO:1, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:19, SEQ ID NO:31 or SEQ ID NO:23, or the complement thereof, under high stringency hybridization conditions.

4. The nucleic acid segment of claim 1, wherein the segment comprises a sequence region of at least 25 contiguous nucleotides from SEQ ID NO:1, or the complement thereof; or wherein the segment specifically hybridizes to the nucleic acid segment of SEQ ID NO:1, or the complement thereof, under high stringency hybridization conditions.

5. The nucleic acid segment of claim 1, wherein the segment comprises a sequence region of at least 25 contiguous nucleotides from SEQ ID NO:29, or the complement thereof; or wherein the segment specifically hybridizes to the nucleic acid segment of SEQ ID NO:29, or the complement thereof, under high stringency hybridization conditions.

6. The nucleic acid segment of claim 1, wherein the segment comprises a sequence region of at least 25 contiguous nucleotides from SEQ ID NO:30, or the complement thereof; or wherein the segment specifically hybridizes to the nucleic acid segment of SEQ ID NO:30, or the complement thereof, under

high stringency hybridization conditions.

7. The nucleic acid segment of claim 1, wherein the segment comprises a sequence region of at least 25 contiguous nucleotides from SEQ ID NO:19, or the complement thereof; or wherein the segment specifically hybridizes to the nucleic acid segment of SEQ ID NO:19, or the complement thereof, under high stringency hybridization conditions.

8. The nucleic acid segment of claim 1, wherein the segment comprises a sequence region of at least 25 contiguous nucleotides from SEQ ID NO:31, or the complement thereof; or wherein the segment specifically hybridizes to the nucleic acid segment of SEQ ID NO:31, or the complement thereof, under high stringency hybridization conditions.

9. The nucleic acid segment of claim 1, wherein the segment comprises a sequence region of at least 25 contiguous nucleotides from SEQ ID NO:23, or the complement thereof; or wherein the segment specifically hybridizes to the nucleic acid segment of SEQ ID NO:23, or the complement thereof, under high stringency hybridization conditions.

10. The nucleic acid segment of claim 1, wherein the segment comprises a sequence region of at least about 30 contiguous nucleotides; or wherein the segment that specifically hybridizes is about 30 nucleotides in length.

11. The nucleic acid segment of claim 10, wherein the segment comprises a sequence region of at least about 50 contiguous nucleotides; or wherein the segment that specifically hybridizes is about 50 nucleotides in length.

12. The nucleic acid segment of claim 11, wherein the segment comprises a sequence region of at least about 100 contiguous nucleotides; or wherein the segment that specifically hybridizes is about 100 nucleotides in length.

13. The nucleic acid segment of claim 12, wherein the segment comprises a sequence region of at least about 200 contiguous nucleotides; or wherein the segment that specifically hybridizes is about 200 nucleotides in length.

14. The nucleic acid segment of claim 13, wherein the segment comprises a sequence region of at least about 500 contiguous nucleotides; or wherein the segment that specifically hybridizes is about 500 nucleotides in length.

15. The nucleic acid segment of claim 14, wherein the segment comprises a sequence regxon that consists of the 1301 contiguous nucleotides of SEQ ID NO:1, or the complement thereof.

16. The nucleic acid segment of claim 14, wherein the segment comprises a sequence region that consists of at least a 1000 nucleotide long contiguous sequence from SEQ ID NO:29, or the complement thereof.

17. The nucleic acid segment of claim 16, wherein the segment comprises a sequence region that consists of the 1882 contiguous nucleotides of SEQ ID NO:29, or the complement thereof.

18. The nucleic acid segment of claim 14, wherein the segment comprises a sequence region that consists of the 1094 contiguous nucleotides of SEQ ID NO:30, or the complement thereof.

19. The nucleic acid segment of claim 14, wherein the segment comprises a sequence region that consists of at least a 1000 nucleotide long contiguous

sequence from SEQ ID NO:19, or the complement thereof.

20. The nucleic acid segment of claim 19, wherein the segment comprises a sequence region that consists of at least a 2000 nucleotide long contiguous sequence from SEQ ID NO:19, or the complement thereof.

21. The nucleic acid segment of claim 20, wherein the segment comprises a sequence region that consists of the 2434 contiguous nucleotides of SEQ ID NO:19, or the complement thereof.

22. The nucleic acid segment of claim 14, wherein the segment comprises a sequence region that consists of the 807 contiguous nucleotides of SEQ ID NO:31, or the complement thereof.

23. The nucleic acid segment of claim 14, wherein the segment comprises a sequence region that consists of at least a 1000 nucleotide long contiguous sequence from SEQ ID NO:23, or the complement thereof.

24. The nucleic acid segment of claim 23, wherein the segment comprises a sequence region that consists of the 2117 contiguous nucleotides of SEQ ID NO:23, or the complement thereof.

25. The nucleic acid segment of claim 1, wherein the segment is up to 10,000 basepairs in length.

26. The nucleic acid segment of claim 25, wherein the segment is up to 5,000 basepairs in length.

27. The nucleic acid segment of claim 26, wherein the segment is up to 1,000 basepairs in length.

28. The nucleic acid segment of claim 27, wherein the segment is up to 500 basepairs in length.

29. The nucleic acid segment of claim 28, wherein the segment is up to 100 basepairs in length.

30. The nucleic acid segment of claim 1, further defined as a DNA segment.

31. The nucleic acid segment of claim 1, further defined as a **RNA** segment.

32. An isolated **RNA** segment of from 25 to about 1,500 nucleotides in length that comprises a non-ciliate **telomerase RNA** template, the **RNA** segment specifically hybridizing to the nucleic acid segment of SEQ ID NO:1 or the complement thereof under high stringency hybridization conditions.

33. The isolated **RNA** segment of claim 32, comprising a yeast **telomerase RNA** template.

34. An affinity column comprising a deoxyoligonucleotide attached to a solid support, wherein the deoxyoligonucleotide includes a GT-rich sequence complementary to the non-ciliate **telomerase RNA** template sequence from position 400 to position 500 of SEQ ID NO:1, and wherein the GT-rich sequence binds to a non-ciliate **telomerase** complex.

35. A DNA segment comprising an isolated gene that encodes a yeast **telomerase RNA** template and includes a contiguous DNA sequence

from position 400 to position 500 of SEQ ID NO:1.

36. The DNA segment of claim 35, comprising an isolated gene that includes a contiguous DNA sequence from position 200 to position 900 of SEQ ID NO:1.

37. The DNA segment of claim 35, comprising an isolated gene that includes the DNA sequence of SEQ ID NO:1.

38. A DNA segment comprising an isolated gene that encodes a polypeptide associated with yeast **telomerase**, wherein the polypeptide includes a contiguous amino acid sequence of at least about twelve amino acids from SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22 or SEQ ID NO:24.

39. The DNA segment of claim 38, comprising an isolated gene that encodes a polypeptide that includes a contiguous amino acid sequence from SEQ ID NO:16.

40. The DNA segment of claim 39, comprising an isolated gene that encodes a polypeptide having the sequence of SEQ ID NO:16.

41. The DNA segment of claim 40, comprising an isolated gene that includes the contiguous DNA sequence from position 54 to position 1799 of SEQ ID NO:29.

42. The DNA segment of claim 38, comprising an isolated gene that encodes a polypeptide that includes a contiguous amino acid sequence from SEQ ID NO:18.

43. The DNA segment of claim 42, comprising an isolated gene that encodes a polypeptide having the sequence of SEQ ID NO:18.

44. The DNA segment of claim 43, comprising an isolated gene that includes the contiguous DNA sequence from position 78 to position 1094 of SEQ ID NO:30.

45. The DNA segment of claim 38, comprising an isolated gene that encodes a polypeptide that includes a contiguous amino acid sequence from SEQ ID NO:20.

46. The DNA segment of claim 45, comprising an isolated gene that encodes a polypeptide having the sequence of SEQ ID NO:20.

47. The DNA segment of claim 46, comprising an isolated gene that includes the contiguous DNA sequence from position 2 to position 2368 of SEQ ID NO:19.

48. The DNA segment of claim 38, comprising an isolated gene that encodes a polypeptide that includes a contiguous amino acid sequence from SEQ ID NO:22.

49. The DNA segment of claim 48, comprising an isolated gene that encodes a polypeptide having the sequence of SEQ ID NO:22.

50. The DNA segment of claim 49, comprising an isolated gene that includes the contiguous DNA sequence from position 55 to position 699 of SEQ ID NO:31.

51. The DNA segment of claim 38, comprising an isolated gene that encodes a polypeptide that includes a contiguous amino acid sequence from SEQ ID NO:24.

52. The DNA segment of claim 51, comprising an isolated gene that encodes a polypeptide having the sequence of SEQ ID NO:24.

53. The DNA segment of claim 52, comprising an isolated gene that includes the contiguous DNA sequence from position 3 to position 1955 of SEQ ID NO:23.

54. The DNA segment of claim 35 or 38, wherein the isolated gene is positioned under the control of a promoter.

55. The DNA segment of claim 54, positioned under the control of a recombinant promoter.

56. The DNA segment of claim 55, further defined as a recombinant vector.

57. A recombinant host cell incorporating a DNA segment in accordance with claim 41 or claim 45.

58. The recombinant host cell of claim 57, further defined as a prokaryotic host cell.

59. The recombinant host cell of claim 57, further defined as a eukaryotic host cell.

60. The recombinant host cell of claim 59, further defined as a yeast cell.

61. The recombinant host cell of claim 59, further defined as a mammalian cell.

62. The recombinant host cell of claim 57, wherein the host cell expresses the DNA segment to produce a **telomerase RNA** template or a polypeptide associated with **telomerase**.

63. The nucleic acid segment of claim 14, wherein the segment comprises a sequence region that consists of about a 1000 nucleotide long contiguous sequence from SEQ ID NO:29, or the complement thereof.

64. The nucleic acid segment of claim 14, wherein the segment comprises a sequence region that consists of about a 1000 nucleotide long contiguous sequence from SEQ ID NO:19, or the complement thereof.

65. The nucleic acid segment of claim 19, wherein the segment comprises a sequence region that consists of about a 2000 nucleotide long contiguous sequence from SEQ ID NO:19, or the complement thereof.

66. The nucleic acid segment of claim 14, wherein the segment comprises a sequence region that consists of about a 1000 nucleotide long contiguous sequence from SEQ ID NO:23, or the complement thereof.

67. The nucleic acid segment of claim 25, wherein the segment is about 10,000 basepairs in length.

68. The nucleic acid segment of claim 26, wherein the segment is about 5,000 basepairs in length.

69. The nucleic acid segment of claim 27, wherein the segment is about 1,000 basepairs in length.

70. The nucleic acid segment of claim 28, wherein the segment is about 500 basepairs in length.

71. The nucleic acid segment of claim 29, wherein the segment is about 100 basepairs in length.

5/7/5 (Item 3 from file: 654)
DIALOG(R)File 654:US PAT.FULL.

02721786
Utility
TELOMERASE ACTIVITY ASSAYS FOR DIAGNOSING PATHOGENIC INFECTIONS

PATENT NO.: 5,695,932
ISSUED: December 09, 1997 (19971209)
INVENTOR(s): West, Michael D., Belmont, CA (California), US (United States of America)
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ASSIGNEE(s): The Regents of the University of California, (A U.S. Company or Corporation), Oakland, CA (California), US (United States of America)
University of Texas System, (A U.S. Company or Corporation), Austin, TX (Texas), US (United States of America)
[Assignee Code(s): 13234; 83960]
APPL. NO.: 8-60,952
FILED: May 13, 1993 (19930513)
This application is a continuation-in-part of Michael D. West et al., entitled "Therapy and diagnosis of conditions related to telomere length and-or **telomerase** activity, filed Mar. 24, 1993, and assigned U.S. Ser. No. 08-038,766, U.S. Pat. No. 5,489,508 which is a continuation-in-part of Michael D. West et al., entitled "**Telomerase** Activity Modulation and Telomere Diagnosis", filed May 13, 1992, and assigned U.S. Ser. No. 07-882,438, abandoned both (including drawings) hereby incorporated by reference herein.

This invention was made with Government support under Grant No. GM-26259, awarded by the National Institute of Health. The Government has certain rights in this invention.

FULL TEXT: 4620 lines

ABSTRACT

Method and compositions are provided for the determination of telomere length and **telomerase** activity, as well as the ability to inhibit **telomerase** activity in the treatment of proliferative diseases. Particularly, primers are elongated under conditions which minimize interference from other genomic sequences, so as to obtain accurate determinations of telomeric length or **telomerase** activity. In addition, compositions are provided for intracellular inhibition of **telomerase** activity and means are shown for slowing the loss of telomeric repeats in aging cells.
We claim:

1. A nucleic acid method for detecting the presence of a eukaryotic pathogen in a patient wherein presence of said eukaryotic pathogen is detected by their **telomerase** activity within a somatic cell population or tissue, comprising the steps of:
obtaining a sample of somatic tissue or cells from said patient;
determining whether **telomerase** activity is present within said sample in said patient; and
correlating presence of **telomerase** activity with presence of said eukaryotic pathogen.

2. A nucleic acid method for detecting the presence of a fungal infection in a patient wherein said fungal infection is detected by their **telomerase** activity within a somatic cell population or tissue, comprising the steps of:
obtaining a sample of somatic tissue or cells from said patient;
determining whether **telomerase** activity is present within said sample in said patient; and
correlating presence of **telomerase** activity with presence of said fungal infection.

3. The method of claim 2, wherein said method further comprises characterizing said fungal infection, by the steps of:
contacting said sample with an oligonucleotide probe complementary to a telomeric nucleic acid sequence of a fungal cell;
allowing said oligonucleotide probe to hybridize to telomeric nucleic acid of a fungal cell contained in said sample;
characterizing said fungal infection as a fungal infection by a particular genus or species of fungus, as measured by specific hybridization of said oligonucleotide probe.

4. The method of claim 3 wherein the fungal cell is of a genus selected from a group consisting of: Candida, Kluyveromyces, and Saccharomyces.

5. The method of claim 4 wherein the telomeric nucleic acid of the fungal cell comprises a sequence selected from the group consisting of:
ACGGATGTCTAAC (SEQ ID NO. 8);
TTCTTGGTGT (SEQ ID NO. 9);
ACGGATGTCACGA (SEQ ID NO. 10);
TCATTGGTGT (SEQ ID NO. 11);
AAGGATGTCACGA (SEQ ID NO. 12);
ACGGATGCAGACT (SEQ ID NO. 13);
CGCTTGGTGT (SEQ ID NO. 14);
ACGGATTTGATTAGTTATGTGGTGT (SEQ ID NO. 15);
ACGGATTTGATTAGGTATGTGGTGT (SEQ ID NO. 16);
CTGGGTGC (SEQ ID NO. 17);
TGTGGGGT (SEQ ID NO. 18);
GTGTAAGGATG (SEQ ID NO. 19); and,
T(G) sub 2-3 (TG) sub 1-6 (SEQ ID NOS. 20, and 47-57).

6. The method of claim 3 wherein the fungal cell is of a genus selected from a group consisting of: Sporothrix, Coccidioides, Histoplasma, Blastomyces, Paracoccidioides, Cryptococcus, Aspergillus, Mucor, and Rizopus.

7. A nucleic acid method for diagnosis of a malarial infection in a patient wherein said malarial infection is an infection by a malarium selected from a group consisting of: Plasmodium vivax, Plasmodium ovale, Plasmodium malariae, and Plasmodium falciparum, wherein said method comprises the steps of:

obtaining a sample of somatic tissue or cells from said patient;
determining whether **telomerase** activity is present within said sample in said patient; and
correlating presence of **telomerase** activity with presence of said malarial infection.

8. The method of claim 1, wherein said determining whether **telomerase** activity is present comprises the steps of:
incubating said cells or tissue in a reaction mixture comprising an oligonucleotide primer that can serve as a substrate for **telomerase**-mediated primer extension, nucleoside triphosphates, and a buffer under conditions such that, if **telomerase** activity is present, said primer is extended by **telomerase**-mediated addition of nucleotides derived from said nucleoside triphosphates to said primer; and,
correlating extension of said primer with the presence of **telomerase** from a pathogen.

5/7/6 (Item 4 from file: 654)
DIALOG(R)File 654:US PAT.FULL.

02711025
Utility
METHODS AND REAGENTS FOR LENGTHENING TELOMERES

PATENT NO.: 5,686,306
ISSUED: November 11, 1997 (19971111)
INVENTOR(s): West, Michael D., San Carlos, CA (California), US (United States of America)
Shay, Jerry, Dallas, TX (Texas), US (United States of America)
Wright, Woodring E., Arlington, TX (Texas), US (United States of America)
ASSIGNEE(s): Board of Regents, The University of Texas System, (A U.S. Company or Corporation), Austin, TX (Texas), US (United States of America)
[Assignee Code(s): 83960]
APPL. NO.: 8-337,684
FILED: November 10, 1994 (19941110)
DISCLAIMER: June 07, 2015 (20150607)

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application is a continuation-in-part of U.S. patent application Ser. Nos. 08-151,477, and 08-153,051, now U.S. Pat. No. 5,618,668, both of which were filed Nov. 12, 1993, which are continuations-in-part of Ser. No. 08-060,952, filed May 13, 1993, which is a continuation-in-part of Ser. No. 08-038,766, filed Mar. 24, 1993, Mar. 10, 1997, now U.S. Pat. No. 5,489,508, which is a continuation-in-part of now abandoned Ser. No. 07-882,438, filed May 13, 1992. Each of the foregoing patent applications is incorporated herein by reference.

FULL TEXT: 1009 lines

ABSTRACT

Method and compositions for increasing telomere length in normal cells can be used to increase the proliferative capacity of cells and to delay the onset of cellular senescence.
We claim:

1. A method for increasing the proliferative capacity of normal cells having **telomerase** activity, which method comprises culturing or cultivating said cells in the presence of an oligonucleotide substrate for **telomerase** under conditions such that said oligonucleotide substrate enters said cells and acts to lengthen telomeric DNA of said cells and the proliferative capacity of said cells is increased.

2. The method of claim 1, wherein said oligonucleotide substrate for **telomerase** consists of an oligonucleotide sequence selected from the group consisting of 5'-TTAGGG-3' (SEQ ID NO 2), 5'-TTAGGGTTA-3'(SEQ ID NO 3), 5'-TTAGGGTTAGGG-3'(SEQ ID NO 1), 5'-TCGAGCACAGTT-3'(SEQ ID NO 4), and 5'-(GXGXGX) sub 2 -3' (SEQ ID NO 5), in which X can be independently selected at each position from either T or A.

3. A method of making human hybridoma cells with increased proliferative capacity, said method comprising:
(a) culturing an immortal cell line in the presence of an oligonucleotide substrate for **telomerase** under conditions such that the telomeres in cells of said cell line lengthen, anti the proliferative capacity of said cells is increased; and
(b) fusing said cells cultured in step (a) with human antibody-producing cells to produce said hybridoma cells.

5/7/7 (Item 5 from file: 654)
DIALOG(R)File 654:US PAT.FULL.

02710965
Utility
METHODS FOR SCREENING FOR AGENTS WHICH MODULATE TELOMERE LENGTH

PATENT NO.: 5,686,245
ISSUED: November 11, 1997 (19971111)
INVENTOR(s): West, Michael D., Belmont, CA (California), US (United States of America)
Shay, Jerry, Dallas, TX (Texas), US (United States of America)
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ASSIGNEE(s): University of Texas System Board of Regents, (A U.S. Company or Corporation), Austin, TX (Texas), US (United States of America)
[Assignee Code(s):
APPL. NO.: 8-475,778
FILED: June 07, 1995 (19950607)
This is a division of application Ser. No. 08-038,766, now issued as U.S. Pat. No. 5,489,508, filed Mar. 24, 1993, hereby incorporated by reference herein in totality, including drawings, which is a continuation-in-part of Michael D. West et al., entitled "**Telomerase** Activity Modulation and Telomere Diagnosis", filed May 13, 1992, and assigned U.S. Ser. No. 07-882,438, now abandoned, hereby incorporated by reference herein.

FULL TEXT: 2429 lines

ABSTRACT

Method and compositions are provided for the determination of telomere length and **telomerase** activity, as well as the ability to inhibit **telomerase** activity in the treatment of proliferative diseases.

Particularly, primers are elongated under conditions which minimize interference from other genomic sequences, so as to obtain accurate determinations of telomeric length or **telomerase** activity. In addition, compositions are provided for intracellular inhibition of **telomerase** activity.

We claim:

1. A method for screening for agents which modulate telomere length, wherein said method comprises the steps of:
(a) contacting cells in vitro with an agent which potential modulates telomere length;
(b) measuring the length of telomeres in cells contacted with said agent and in cells not contacted with said agent, and
(c) correlating a difference in telomere length in cells contacted with said agent as compared to cells not contacted with said agent identification of an agent which modulates telomere length.

2. The method of claim 1, wherein said cells are human cells.

3. The method of claim 1, wherein said cells are immortal cells.

4. The method of claim 1, wherein the difference in telomere length of step (c) is that the length of telomeres in cells contacted with said agent is greater than the length of telomeres in cells not contacted with said agent.

5. The method of claim 1, wherein the difference in telomere length of step (c) is that the length of telomeres in cells contacted with said agent is less than the length of telomeres in cells not contacted with said agent.

6. The method of claim 1, wherein the measuring of step (b) comprises the steps of:
(a) digesting genomic DNA of said cells to obtain terminal restriction fragments;
(b) separating said terminal restriction fragments by size;
(c) hybridizing an oligonucleotide probe complementary to telomeric DNA under conditions such that said probe hybridizes specifically to telomeric DNA in said terminal restriction fragments;
(d) measuring amount of bound probe; and
(e) correlating mount of bound probe with telomere length.

7. The method of claim 1, wherein the measuring of step (b) comprises the steps of:
(a) adding a primer sufficiently complementary to a 3'-end of a telomere in double-stranded chromosomal DNA of said cells to hybridize specifically thereto under conditions such that said primer is extended by an agent for polymerization until reaching a non-telomeric deoxynucleotide to form a primer extension product complementary to telomeric DNA; and
(b) measuring primer extension product size to provide a measure of telomere length.

8. The method of claim 1, wherein the measuring of step (b) comprises the steps of:
(a) denaturing cellular DNA of said sample in situ;
(b) adding an oligonucleotide probe labeled with a detectable label and complementary to telomeric DNA to said denatured DNA under conditions such that said probe anneals to said DNA;
(c) measuring signal intensity of said label from said probe annealed to

said denatured DNA; and
(d) correlating said signal intensity with telomere length.

9. The method of claim 1, wherein said cells are cancer cells.

5/7/8 (Item 6 from file: 654)
DIALOG(R)File 654:US PAT.FULL.

02665738
Utility
THERAPY AND DIAGNOSIS OF CONDITIONS RELATED TO TELOMERE LENGTH AND/OR **TELOMERASE** ACTIVITY

PATENT NO.: 5,645,986
ISSUED: July 08, 1997 (19970708)
INVENTOR(s): West, Michael D., San Carlos, CA (California), US (United States of America)
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Geron Corporation, (A U.S. Company or Corporation), Menlo Park , CA (California), US (United States of America)
The Reagents of the University of California, (A U.S. Company or Corporation), Oakland, CA (California), US (United States of America)
[Assignee Code(s): 13234; 37860; 83960]
APPL. NO.: 8-153,051
FILED: November 12, 1993 (19931112)
This application is a continuation-in-part of Michael D. West et al., entitled "Therapy and diagnosis of conditions related to telomere length and-or **telomerase** activity, filed May 13, 1993, and assigned U.S. Ser. No. 08-060,952 (hereby incorporated by reference herein), which is a continuation-in-part of Michael D. West et al., entitled "Therapy and diagnosis of conditions related to telomere length and-or **telomerase** activity," filed Mar. 24, 1993, and assigned U.S. Ser. No. 08-038,766, now U.S. Pat. No. 5,489,508 which is a continuation-in-part of Michael D. West et al., entitled "**Telomerase** Activity Modulation and Telomere Diagnosis", filed May 13, 1992, and assigned U.S. Ser. No. 07-882,438, abandoned, all (including drawings) hereby incorporated by reference herein.

This invention was made with Government support under Grant No. GM-26259, awarded by the National Institute of Health. The Government has certain rights in this invention.

FULL TEXT: 5702 lines

ABSTRACT

Method and compositions are provided for the determination of telomere length and **telomerase** activity, as well as the ability to increase or decrease **telomerase** activity in the treatment of proliferative diseases. Particularly, primers are elongated under conditions which minimize interference from other genomic sequences, so as to obtain accurate determinations of telomeric length or **telomerase** activity. In addition, compositions are provided for intracellular inhibition of **telomerase** activity and means are shown for slowing or reversing the loss of telomeric repeats in aging cells.

We claim:

1. Method for screening for an agent which inhibits **telomerase** activity, comprising the steps of

combining in a reaction mixture a potential said agent, an active **telomerase**, a substrate oligonucleotide for said **telomerase**, and nucleotide triphosphates;

incubating said reaction mixture for a predetermined time for said substrate oligonucleotide to be extended;

determining whether extended substrate oligonucleotide is formed by contacting products of said reaction mixture with an oligonucleotide probe which hybridizes to a telomere repeat sequence; and

comparing hybridization of said probe to said products with hybridization of said probe to products of a reaction mixture in which said agent is not present; and,

correlating reduced hybridization in presence of said agent compared with hybridization observed in absence of said agent with inhibition of **telomerase** activity by said agent.

2. Method of screening for an agent which inhibits human **telomerase** comprising the steps of: contacting human **telomerase** with a potential said agent in the presence of a biotin-labelled substrate oligonucleotide; incubating under conditions in which said **telomerase** will extend said oligonucleotide in the absence of said inhibitor; capturing any extended substrate oligonucleotide on an avidinylated solid support; contacting said oligonucleotide substrate with an oligonucleotide probe which hybridizes to a telomere repeat sequence; comparing hybridization of said probe to said oligonucleotide substrate with hybridization of said probe to products of a reaction mixture in which said agent is not present; and, correlating reduced hybridization in presence of said agent compared with hybridization observed in absence of said agent with inhibition of **telomerase** activity by said agent.

3. Method of claim 1 wherein said active **telomerase** is human **telomerase**.

4. Method of claim 1 wherein said active **telomerase** is fungal **telomerase**.

5. The method of claim 1 wherein said active **telomerase** is Tetrahymena **telomerase**.

6. The method of claim 1 wherein said method comprises immobilizing the products of the reaction mixture on a solid support.

7. The method of claim 1 wherein said test compound is an inhibitor of retrovital reverse transcriptase.

8. The method of claim 1 wherein said test compound is an oligonucleotide.

9. The method of claim 6 wherein said oligonucleotide template is labeled with a compound which facilitates binding of said oligonucleotide template to said solid support.

10. The method of claim 1 wherein said substrate oligonucleotide comprises a telomere repeat sequence.

11. The method of claim 1 wherein said substrate oligonucleotide is a sequence 5' TTAGGGTTAGGGTTAGGG 3' (SEQ ID NO. 5).

12. The method of claim 1 wherein said substrate oligonucleotide is a sequence 5' GTTAGGGTTAGGGTTAGG 3' (SEQ ID NO. 31).

13. The method of claim 1 wherein said substrate oligonucleotide is a sequence 5' AATCCGTCGAGCAGAGTT 3' (SEQ ID NO. 32).

14. The method of claim 2 wherein said substrate oligonucleotide is a sequence 5' TTAGGGTTAGGGTTAGGG 3' (SEQ ID NO. 5).

15. The method of claim 2 wherein said substrate oligonucleotide is a sequence 5' GTTAGGGTTAGGGTTAGG 3' (SEQ ID NO. 31).

16. The method of claim 2 wherein said substrate oligonucleotide is a sequence 5' AATCCGTCGAGCAGAGTT 3' (SEQ ID NO. 32).

17. The method of claim 9 wherein said compound is biotin.

18. The method of claim 1 wherein said oligonucleotide probe is labeled with a radioisotope.

19. The method of claim 2 wherein said oligonucleotide probe is labeled with a radioisotope.

20. The method of claim 18 wherein said radioisotope is sup 32 P.

21. The method of claim 19 wherein said radioisotope is sup 32 P.

22. The method of claim 1 wherein said oligonucleotide probe is labeled with a fluorescent label.

23. The method of claim 1 wherein said oligonucleotide probe is labeled with an epitope for an antibody.

24. The method of claim 23 wherein said epitope is dioxygenin.

25. The method of claim 2 wherein said oligonucleotide probe is labeled with a fluorescent label.

26. The method of claim 2 wherein said oligonucleotide probe is labeled with an epitope for an antibody.

27. The method of claim 26 wherein said antibody is dioxygenin.

02647322
Utility
TELOMERASE ACTIVITY ASSAYS

PATENT NO.: 5,629,154
ISSUED: May 13, 1997 (19970513)
INVENTOR(s): Kim, Nam W., Santa Clara, CA (California), US (United States of America)
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ASSIGNEE(s): Geron Corporation, (A U.S. Company or Corporation), Menlo Park , CA (California), US (United States of America)
[Assignee Code(s): 37860]
APPL. NO.: 8-315,214
FILED: September 28, 1994 (19940928)

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of copending Ser. No. 08-255,774, filed 7 Jun. 1994; which is a continuation-in-part of copending application Ser. No. 08-151,477, filed 12 Nov. 1993; and which is a continuation-in-part of copending application Ser. No. 08-153,051, filed 12 Nov. 1993.

FULL TEXT: 1693 lines

ABSTRACT

Telomerase activity in a sample can be measured using a two reaction protocol involving **telomerase** substrate and primer extension steps.
We claim:

1. A method for determining whether a cell sample contains **telomerase** activity, said method comprising the steps of:
(a) preparing a cell extract from said cell sample;
(b) placing an aliquot of said cell extract in a reaction mixture comprising a **telomerase** substrate lacking a telomeric repeat sequence and a buffer in which **telomerase** can catalyze extension of said **telomerase** substrate by addition of telomeric repeat sequences;
(c) adding to said reaction mixture a primer comprising a sequence sufficiently complementary to a telomeric repeat to hybridize specifically thereto under conditions such that if an extended **telomerase** substrate is present in said reaction mixture, said primer will hybridize to said extended **telomerase** substrate and extend to form a complementary copy of said extended **telomerase** substrate, thereby forming duplex DNA molecules comprising an extended **telomerase** substrate bound to an extended primer; and
(d) correlating presence of **telomerase** activity in said cell sample with presence of duplex DNA molecules comprising an extended **telomerase** substrate bound to an extended primer and absence of **telomerase** activity in said cell sample with absence of said duplex DNA molecules.

2. The method of claim 1, wherein step (c) additionally comprises steps of:
(1) heating said reaction mixture to denature said duplex DNA molecules; and

(2) cooling said reaction mixture to a temperature at which complementary nucleic acids can hybridize and said primer can extend if extended **telomerase** substrates are present.

3. The method of claim 2, wherein said heating and cooling steps are repeated at least 5 times, and said primer is present in amounts sufficient for the formation of extended primers during each cooling step.

4. The method of claim 2, wherein a template-dependent DNA polymerase is present in the reaction mixture of step (c) of claim 1 and said primer is extended by addition of nucleotides to said primer by said DNA polymerase.

5. The method of claim 2, wherein a template-dependent DNA ligase is present in the reaction mixture of step (c) of claim 1 and said primer is extended by ligation of an oligonucleotide ligomer to said primer by said DNA ligase.

6. The method of claim 3, wherein a thermostable template-dependent DNA polymerase is present in the reaction mixture of step (c) of claim 1 and said primer is extended by addition of nucleotides to said primer by said DNA polymerase.

7. The method of claim 3, wherein a thermostable template-dependent DNA ligase is present in the reaction mixture of step (c) of claim 1 and said primer is extended by ligation of an oligonucleotide ligomer to said primer by said DNA ligase.

8. The method of claim 3, wherein said cell extract is prepared by lysing cells in said cell sample in a buffer comprising a non-ionic or zwitterionic detergent.

9. The method of claim 3, wherein said cell sample is a human cell sample.

10. The method of claim 3, wherein said primer is initially kept separate from said cell extract by a wax barrier, and said reaction mixture is heated to melt said wax barrier and add said primer to said reaction mixture.

11. The method of claim 3, wherein said reaction mixture comprises a labelled **telomerase** substrate.

12. The method of claim 3, wherein said reaction mixture comprises a labelled primer.

13. The method of claim 3, wherein said reaction mixture comprises a labelled nucleoside triphosphate.

14. The method of claim 6, wherein said **telomerase** substrate and said primer have sequences that do not substantially bind to one another to form a dimer of said substrate and said primer during said primer extension step.

15. The method of claim 6, wherein said primer comprises a non-telomeric repeat sequence at a 5'-end of said primer.

16. The method of claim 6, wherein said primer comprises at least 2 telomeric repeat sequences.

17. The method of claim 7, wherein said primer and ligomer are initially

kept separate from said cell extract by a wax barrier and said reaction mixture is heated to melt said wax barrier and add said primer and said ligomer to said reaction mixture.

18. The method of claim 9, wherein said **telomerase** substrate lacking a telomeric repeat sequence is oligonucleotide TS (SEQ ID NO. 1).

19. The method of claim 9, wherein said primer is CX (SEQ ID NO. 2) or ACT (SEQ ID NO. 3).

20. The method of claim 12, wherein said label is selected from the group consisting of a radioactive molecule, a fluorescent molecule, a phosphorescent molecule, a ligand for a receptor, biotin, and avidin.

21. The method of claim 3, wherein said primer of step (c) comprises a sequence at its 5' end that is non-complementary to a telomeric repeat sequence.

22. The method of claim 1, wherein said buffer is a buffer in which a template-dependent DNA polymerase or template-dependent DNA ligase can extend said primer by the addition of nucleotides or oligonucleotide ligomers.

23. The method of claim 22, wherein said buffer is an aqueous solution having about 20 mM Tris-HCl, pH 8.3, 1.5 mM MgCl sub 2, 63 mM KCl, 0.005% Tween 20, and 1 mM EGTA.

5/7/10 (Item 8 from file: 654)
DIALOG(R)File 654:US PAT.FULL.

02495931
Utility
THERAPY AND DIAGNOSIS OF CONDITIONS RELATED TO TELOMERE LENGTH AND/OR **TELOMERASE** ACTIVITY
[Detecting cancer in humans by determining whether oligonucleotide primer is extended when incubated with cell sample, nucleoside triphosphates, buffer]

PATENT NO.: 5,489,508
ISSUED: February 06, 1996 (19960206)
INVENTOR(s): West, Michael D., Belmont, CA (California), US (United States of America)
Shay, Jerry, Dallas, TX (Texas), US (United States of America)
Wright, Woodring, Arlington, TX (Texas), US (United States of America)
ASSIGNEE(s): University of Texas System Board of Regents, (A U.S. Company or Corporation), Austin, TX (Texas), US (United States of America)
[Assignee Code(s): 83960]
APPL. NO.: 8-38,766
FILED: March 24, 1993 (19930324)
This application is a continuation-in-part of Michael D. West et al., entitled "**Telomerase** Activity Modulation and Telomere Diagnosis", filed May 13, 1992, and assigned U.S. Ser. No. 07-882,438, abandoned, hereby incorporated by reference herein.

FULL TEXT: 2370 lines

ABSTRACT

Method and compositions are provided for the determination of telomere length and **telomerase** activity, as well as the ability to inhibit **telomerase** activity in the treatment of proliferative diseases. Particularly, primers are elongated under conditions which minimize interference from other genomic sequences, so as to obtain accurate determinations of telomeric length or **telomerase** activity. In addition, compositions are provided for intracellular inhibition of **telomerase** activity.

We claim:

1. A method for detecting cancer in a human, said method comprising:
(a) obtaining a cell sample from said individual;
(b) lysing cells in said cell sample to form a cell lysate under conditions such that denaturation of **telomerase** does not occur;
(c) incubating an aliquot of said cell lysate in a reaction mixture comprising an oligonucleotide primer that can serve as a substrate for **telomerase**-mediated primer extension, nucleoside triphosphates, and a buffer under conditions such that, if **telomerase** activity is present, said primer is extended by **telomerase** -mediated addition of nucleotides derived from said nucleoside triphosphates to said primer;
(d) determining whether said primer has been extended; and
(e) correlating presence of an extended primer with presence of cancer cells in said human and absence of an extended primer with absence of cancer cells in said human.

2. The method of claim 1, wherein step (d) further comprises separating primers from other nucleic acids in said sample.

3. The method of claim 1, wherein said primer comprises a label that facilitates detection of extended primers or separation of primers from other nucleic acids in said sample.

4. The method of claim 1, wherein said nucleoside triphosphates are dATP, dTTP, and dGTP.

5. The method of claim 1, wherein said human has already been diagnosed as having a tumor, and said cell sample is obtained from a site at a margin of said tumor in said human.

6. The method of claim 1, wherein said human has already been diagnosed as having a tumor, and said cell sample is obtained from said tumor.

7. The method of claim 4, wherein one of said nucleoside triphosphates is labelled.

8. The method of claim 4, wherein said label is selected from the group of labels consisting of radiolabels, enzymes, and fluorescent labels.

9. The method of claim 8, wherein said label is sup 32 P.

10. The method of claim 9, wherein said nucleoside triphosphates are dATP, dTTP, and sup 32 P-dGTP.

11. The method of claim 10, wherein said primer is 5'-TTAGGGTTAGGGTTAGGG-3' (SEQ ID NO. 5).

02470421
Utility

MODULATION OF PIF-1-TYPE HELICASES
[Identifying controllers of telomere formation or elongation]

PATENT NO.: 5,466,576
ISSUED: November 14, 1995 (19951114)
INVENTOR(s): Schulz, Vincent P., Seattle, WA (Washington), US (United States of America)
Zakian, Virginia A., Seattle, WA (Washington), US (United States of America)
ASSIGNEE(s): Fred Hutchinson Cancer Research Center, (A U.S. Company or Corporation), Seattle, WA (Washington), US (United States of America)
[Assignee Code(s): 14990]
APPL. NO.: 8-86,993
FILED: July 02, 1993 (19930702)

The invention described in this application may have had U.S. government support from National Institutes of Health grants GM-26938 and GM-43265. The U.S. government may have certain rights in the invention.

FULL TEXT: 1388 lines

ABSTRACT

Method for affecting viability of a eucaryotic cell by contacting the cell with a modulator of the activity of a PIF-1-type helicase in the cell. Such contacting specifically increases or decreases the specific activity of the helicase in the cell.

We claim:

1. A method for identifying a modulator of telomere formation or elongation, comprising the steps of:
contacting a potential modulator of telomere formation or elongation with a PIF-1-type helicase in the presence of cells, and assaying the activity of said PIF-1-type helicase in vitro or in vivo, wherein said modulator specifically increases or decreases said activity and thereby modulates said telomere formation or elongation.

2. The method of claim 1, wherein the PIF-1-type helicase affects telomere function but not mitochondrial function.

3. The method of claim 1, wherein telomere length or heterogeneity are assayed to determine the activity of said PIF-1-type helicase.

4. The method of claim 3, wherein inhibition of activity of said PIF-1-type helicase is determined by an increase in telomere length.

5. The method of claim 1, wherein loss of subtelomeric genes is monitored to determine the activity of said PIF-1-type helicase.

6. The method of claim 1, wherein altered specificity of telomere formation is monitored to determine the activity of said PIF-1-type helicase.

7. The method of claim 1, wherein increased de novo telomere formation on a broken chromosome is monitored to determine the activity of said PIF-1-type helicase.

8. A modulator of telomere formation or elongation which specifically increases or decreases the activity Of PIF-1-type helicase, said modulator identified by the method of claim 1 that is specific for telomere function and not mitochondrial function.

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     $3.00  Estimated cost FilePause
            $0.12    0.002 Hrs File5
               $2.90  2 Type(s) in Format  7
            $2.90  2 Types
     $3.02  Estimated cost File5
            $0.06    0.002 Hrs File155
     $0.06  Estimated cost File155
            $0.00    0.000 Hrs File357
     $0.00  Estimated cost File357
            $0.24    0.002 Hrs File399
     $0.24  Estimated cost File399
            $0.22    0.001 Hrs File351
     $0.22  Estimated cost File351
            $6.72    0.056 Hrs File654
              $33.75  9 Type(s) in Format  7
           $33.75  9 Types
    $40.47  Estimated cost File654
            OneSearch, 6 files,  0.166 Hrs FileOS
    $47.01  Estimated cost this search
    $47.61  Estimated total session cost   0.184 Hrs.

SYSTEM:OS  - DIALOG OneSearch
  File   5:BIOSIS PREVIEWS(R)  1969-1998/Feb W2
         (c) 1998 BIOSIS
  File 155:MEDLINE(R)  1966-1998/Apr W1
         (c) format only 1998 Dialog Corporation
*File 155: Due to technical problems, 1998 MEDLINE has been
           restored to the 1997 version.
  File 357:Derwent Biotechnology Abs  1982-1998/Feb B2
         (c) 1998 Derwent Publ Ltd
  File 399:CA SEARCH(R)  1967-1998/UD=12807
         (c) 1998 American Chemical Society
*File 399: Use is subject to the terms of your user/customer agreement.
RANK charge added; see HELP RATES 399.

      Set  Items  Description
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? s pfiesteria

      S1      19  PFIESTERIA
? rd
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...completed examining records
S2 16 RD (unique items)
? t s2/7/all

2/7/1 (Item 1 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

14084619 BIOSIS Number: 01084619
Impacts of a coastal river and estuary from rupture of a large swine waste holding lagoon
Burkholder J M; Mallin M A; Glasgow H B Jr; Larsen L M; McIver M R; Shank G C; Deamer-Melia N; Briley D S; Springer J; Touchette B W; Hannon E K
Dep. Botany, North Carolina State Univ., Box 7612, Raleigh, NC 27695-7612, USA
Journal of Environmental Quality 26 (6). 1997. 1451-1466.
Full Journal Title: Journal of Environmental Quality
ISSN: 0047-2425
Language: ENGLISH
Print Number: Biological Abstracts Vol. 105 Iss. 004 Ref. 056894
We tracked a swine waste spill (4.13 times 10-7 L) into a small receiving river and estuary. After 2 d, a 29-km freshwater segment that the wastes had traversed was anoxic, with ca. 4000 dead fish floating and hung in shoreline vegetation. Suspended solids, nutrients, and fecal coliforms were 10- to 10-0-fold higher at the plume's edge (71.7 mg SS/L, 39.6 mg NH-4+-N/L, and gt 1 x 10-6 cfu/10-0 mL, respectively; cfu, colony forming units, SS; suspended solids) than in unaffected reference sites. Elevated nutrients and an oxygen sag from the plume reached the main estuary after ca. 5 d. Increased phytoplankton production was contributed by noxious algae, Synechococcus aeruginosa and Phaeocystis globosa (10-8 and 10-6 cells/mL, respectively) after 7 to 14 d. The toxic dinoflagellates, **Pfiesteria** piscicida and a second **Pfiesteria**-like species, increased to potentially lethal densities (10-3 cells/mL) that coincided with a fish kill and ulcerative epizootic. After 14 d, water-column fecal coliforms generally were at 10-2 to 10-3 cfu/ 10-0 mL. But where the plume had hovered for the first 5 d, surface sediments mostly yielded gtoreq 10-4 cfu/10-0 mL slurry, and after 61 d densities in surficial sediments were still at 10-3 to 10-4 cfu/100 mL. Dinoflagellate and euglenoid blooms developed and moved downestuary, where they were detected after 61 d. This study documented acute impacts to surfacewaters from a concentrated swine operation, and examined some environmental policies affecting the intensive animal operation industry.

2/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

14045507 BIOSIS Number: 01045507
Pfiesteria piscicida and other **Pfiesteria**-like dinoflagellates: Behavior, impacts, and environmental controls
Burkholder J M; Glasgow H B Jr
Dep. Botany, Box 7612, North Carolina State Univ., Raleigh, NC 27695-7612, USA
Limnology and Oceanography 42 (5 PART 2). 1997. 1052-1075.
Full Journal Title: Limnology and Oceanography
ISSN: 0024-3590
Language: ENGLISH
Print Number: Biological Abstracts Vol. 105 Iss. 003 Ref. 032065

Toxic **Pfiesteria** -like dinoflagellates have been implicated as causative agents of major fish kills (affecting 10-3109 fish) in estuaries and coastal waters of the mid-Atlantic and southeastern U.S. Transformations among an array of flagellated, amoeboid, and encysted stages in the complex life cycle of the representative species, **Pfiesteria** piscicida, are controlled by the availability of fresh secretions, blood, or other tissues of fish prey. P. piscicida also is a voracious predator on other estuarine microorganisms. **Pfiesteria**-like dinoflagellates require an unidentified substance(s) commonly found in fresh fish excreta-secreta to initiate toxin production. P. piscicida is lethal to fish at low cell densities (gt 250-300 cells ml-1), and at sublethal levels (apprx 100-250 cells ml-1) it has been shown to cause ulcerative fish diseases. P. piscicida also has been linked to serious human health impacts. This dinoflagellate is eurythermal and euryhaline, with optima for toxic activity by the most lethal stage (toxic zoospores, TZs) at gtoreq 26 degree C and 15 psu, respectively. Thus far it has shown no light optimum and is capable of killing fish at any time during a 24-h cycle. In warmer waters (gtoreq 15 degree C) flagellated stages predominate while fish are dying, whereas amoebae predominate in colder conditions and when fish are dead. Nutritional stimuli influencing P. piscicida are complex; inorganic phosphate apparently can directly stimulate TZs, whereas inorganic phosphate and nitrate indirectly promote increased production of nontoxic zoospores (NTZs, maintained in the absence of live fish, as potential precursors to lethal TZs) by stimulating their algal prey. Organic phosphate (P-o) and nitrogen are taken up by P. piscicida osmotrophically, and P-o is stimulatory to both TZs and NTZs. The available data point to a critical need to characterize the chronic and acute impacts of toxic **Pfiesteria**-like dinoflagellates on fish and other targeted prey in estuarine and coastal waters that are adversely affected by cultural eutrophication.

2/7/3 (Item 3 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

13608196 BIOSIS Number: 99608196
Trophic controls on stage transformations of a toxic ambush-predator dinoflagellate
Burkholder J M; Glasgow H B Jr
Dep. Botany, Box 7612, North Carolina State Univ., Raleigh, NC 27695, USA
Journal of Eukaryotic Microbiology 44 (3). 1997. 200-205.
Full Journal Title: Journal of Eukaryotic Microbiology
ISSN: 1066-5234
Language: ENGLISH
Print Number: Biological Abstracts Vol. 104 Iss. 003 Ref. 034210
The toxic dinoflagellate, **Pfiesteria** piscicida, was recently implicated as the causative agent for about 50% of the major fish kills occurring over a three-year period in the Albemarle-Pamlico Estuarine System of the southeastern USA. Transformations between life-history stages of this dinoflagellate are controlled by the availability of fresh fish secretions or fish tissues, and secondarily influenced by the availability of alternate prey including bacteria, algae, microfauna, and mammalian tissues. Toxic zoospores of P. piscicida subdue fish by excreting lethal neurotoxins that narcotize the prey, disrupt its osmoregulatory system, and attack its nervous system. While prey are dying, the zoospores feed upon bits of fish tissue and complete the sexual phase of the dinoflagellate life cycle. Other stages in the complex life cycle of P. piscicida include cryptic forms of filose, rhizopodial, and lobose amoebae that can form within minutes from toxic zoospores, gametes, or planozygotes. These

cryptic amoebae feed upon fish carcasses and other prey and, thus far, have proven less vulnerable to microbial predators than flagellated life-history stages. Lobose amoebae that develop from toxic zoospores and planozygotes during colder periods have also shown ambush behavior toward live fish. In the presence of abundant flagellated algal prey, amoeboid stages produce nontoxic zoospores that can become toxic and form gametes when they detect what is presumed to be a threshold level of a stimulatory substance(s) derived from live fish. The diverse amoeboid stages of this fish "ambush-predator" and at least one other **Pfiesteria**-like species are ubiquitous and abundant in brackish waters along the western Atlantic and Gulf Coasts, indicating a need to re-evaluate the role of dinoflagellates in the microbial food webs of turbid nutrient-enriched estuaries.

2/7/4 (Item 4 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

13167494 BIOSIS Number: 99167494
Effects of the toxic dinoflagellate, **Pfiesteria** piscicida, on juvenile bay scallops (Argopecten irradians, Lamarck)
Springer J J; Burkholder J; Shumway S E
Dep. Botany, N.C. State Univ., Raleigh, NC 27695, USA
Journal of Shellfish Research 15 (2). 1996. 530.
Full Journal Title: 88th Annual Meeting of the National Shellfisheries Association, Baltimore, Maryland, USA, April 14-18, 1996. Journal of Shellfish Research
ISSN: 0730-8000
Language: ENGLISH
Print Number: Biological Abstracts/RRM Vol. 048 Iss. 010 Ref. 174097

2/7/5 (Item 5 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

13028359 BIOSIS Number: 99028359
Effects on fisheries and human health linked to a toxic estuarine dinoflagellate
Burkholder J M; Glasgow H B Jr
N.C. State Univ., Raleigh, NC 27965-7612, USA
Toxicon 34 (3). 1996. 308.
Full Journal Title: Fifth Pan American Symposium on Animal, Plant and Microbial Toxins, Frederick, Maryland, USA, July 30-August 4, 1995. Toxicon
ISSN: 0041-0101
Language: ENGLISH
Print Number: Biological Abstracts/RRM Vol. 048 Iss. 007 Ref. 122095

2/7/6 (Item 6 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

13003809 BIOSIS Number: 99003809
Ocean commotion
Tibbetts J
Environmental Health Perspectives 104 (4). 1996. 380-385.
Full Journal Title: Environmental Health Perspectives
ISSN: 0091-6765

Language: ENGLISH
Print Number: Biological Abstracts Vol. 102 Iss. 001 Ref. 003809

2/7/7 (Item 7 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

12125532 BIOSIS Number: 98725532
Fish kills linked to a toxic ambush-predator dinoflagellate: Distribution and environmental conditions
Burkholder J M; Glasgow H B Jr; Hobbs C W
Dep. Botany, Box 7612, N.C. State Univ., Raleigh, NC 27695-7612, USA
Marine Ecology Progress Series 124 (1-3). 1995. 43-61.
Full Journal Title: Marine Ecology Progress Series
ISSN: 0171-8630
Language: ENGLISH
Print Number: Biological Abstracts Vol. 101 Iss. 008 Ref. 109807
The toxic ambush-predator dinoflagellate **Pfiesteria** piscicida gen. et sp. nov. has been implicated as a causative agent of major fish kills in estuarine ecosystems of the southeastern United States. P. piscicida is stimulated by fresh fish secreta, and it was lethal to all 19 species of native and exotic finfish and shellfish bioassayed in culture; thus far in field and aquaculture kills linked to the dinoflagellate, 13 additional fish species have been affected. Field data in combination with confirming laboratory bioassays documented toxicity at temperatures ranging from 12 to 33 degree C, with most outbreaks occurring at 26 degree C or higher. P. piscicida also exhibits wide salinity tolerance; it was lethal to fish from 0 to 35 ppt in calcareous waters, with an optimum salinity for growth and toxic activity at 15 ppt. It was toxic to fish day or night (gtoreq 250 toxic zoospores ml-1) without an apparent light optimum, in experimental laboratory conditions ranging from 0.2 mu-Ein m-2s-1 (darkness for all but 30 to 60 s at 20 mu-Ein m-2 s-1 per 24 h period) to 200 mu-Ein m-2s-1 (12:12 h light:dark cycle). Moreover, field fish kills have occurred in darkness and at light intensities up to 2400 mu-Ein m-2s-1. Through direct microscope counts of water samples, confirmed identifications with scanning electron microscopy, and confirmed toxic activity in bioassays, P. piscicida was implicated as the causative agent of 52 +- 7% of the major fish kills (affecting 103 to 109 fish from May 1991 to November 1993) on an annual basis in North Carolina estuaries and coastal waters. Since their discovery in natural habitat during 1991, **Pfiesteria**-like species also have been tracked to eutrophic sudden-death fish kill sites in estuaries, coastal waters, and aquaculture facilities from the mid-Atlantic through the Gulf Coast. Toxic ambush-predator dinoflagellates likely are widespread in warm temperate/subtropical regions, acting as significant but often undetected sources of fish mortality and disease.

2/7/8 (Item 8 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

12122850 BIOSIS Number: 98722850
Pfiesteria piscicida gen. ET sp. nov. (Pfiesteriaceae FAM. nov.), a new toxic dinoflagellate with a complex life cycle and behavior
Steidinger K A; Burkholder J M; Glasgow H B Jr; Hobbs C W; Garrett J K; Truby E W; Noga E J; Smith S A
Florida Marine Res. Inst., Dep. Environmental Protection, 100 Eighth Avenue S.E., St. Petersburg, FL 33701, USA
Journal of Phycology 32 (1). 1996. 157-164.

Full Journal Title: Journal of Phycology
ISSN: 0022-3646
Language: ENGLISH
Print Number: Biological Abstracts Vol. 101 Iss. 008 Ref. 107125

The newly described toxic dinoflagellate **Pfiesteria** piscicida is a polymorphic and multiphasic species with flagellated, amoeboid, and cyst stages, The species is structurally a heterotroph; however, the flagellated stages can have cleptochloroplasts in large food vacuoles and can temporarily function as mixotrophs. The flagellated stage has a typical mesokaryotic nucleus, and the theca is composed of four membranes, two of which are vesicular and contain thin plates arranged in a Kofoidian series of Po, cp, X, 4', 1a, 5'', 6c, 4s, 5''', and 2''''. The plate tabulation is unlike that of any other armored dinoflagellate. Nodules often demark the suture lines underneath the outer membrane, but fixation protocols can influence the detection of plates. Amoeboid benthic stages can be filose to lobose, are thecate, and have a reticulate or spiculate appearance. Amoeboid stages have a eukaryotic nuclear profile and are phagocytic. Cyst stages include a small spherical stage with a honeycomb, reticulate surface and possibly another stage that is elongate and oval to spherical with chrysophyte-like scales that can have long bracts. The species is placed in a new family, Pfiesteriaceae, and the order Dinamoebales is emended.

2/7/9 (Item 9 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

12115863 BIOSIS Number: 98715863
Behavior of a toxic estuarine dinoflagellate with microbial and vertebrate prey
Burkholder J M; Glasgow H B Jr
Dep. Botany, Box 7612, North Carolina State Univ., Raleigh, NC 27695, USA
Journal of Eukaryotic Microbiology 43 (1). 1996. 1A.
Full Journal Title: 48th Annual Meeting of the Society of Protozoologists, June 27-30, 1995. Journal of Eukaryotic Microbiology
ISSN: 1066-5234
Language: ENGLISH
Print Number: Biological Abstracts/RRM Vol. 048 Iss. 004 Ref. 062045

2/7/10 (Item 10 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

12014314 BIOSIS Number: 98614314
Insidious effects of a toxic estuarine dinoflagellate on fish survival and human health
Glasgow H B Jr; Burkholder J M; Schmechel D E; Tester P A; Rublee P A
Dep. Botany, Box 7612, North Carolina State University, Raleigh, NC 27695-7612, USA
Journal of Toxicology and Environmental Health 46 (4). 1995. 501-522.
Full Journal Title: Journal of Toxicology and Environmental Health
ISSN: 0098-4108
Language: ENGLISH
Print Number: Biological Abstracts Vol. 101 Iss. 003 Ref. 042019

The estuarine dinoflagellate **Pfiesteria** piscicida gen. et sp. nov. produces exotoxin(s) that can be absorbed from water or fine aerosols. Culture filtrate (0.22 mu-m porosity filters, gt 250 toxic flagellated cells/ml) induces formation of open ulcerative sores, hemorrhaging, and death of finfish and shellfish. Human exposure to aerosols from

ichthyotoxic cultures (gtoreq 2000 cells/ml) has been associated with narcosis, respiratory distress with asthma-like symptoms, severe stomach cramping, nausea, vomiting, and eye irritation with reddening and blurred vision (hours to days); autonomic nervous system dysfunction (localized sweating, erratic heart beat (weeks)); central nervous system dysfunction (sudden rages and personality change (hours to days), and reversible cognitive impairment and short-term memory loss (weeks)), and chronic effects including asthma-like symptoms, exercise fatigue, and sensory symptoms (tingling or numbness in lips, hands, and feet; months to years). Elevated hepatic enzyme levels and high phosphorus excretion in one human exposure suggested hepatic and renal dysfunction (weeks); easy infection and low counts of several T-cell types may indicate immune system suppression (months to years). **Pfiesteria** piscicida is euryhaline and eurythermal, and in bioassays a nontoxic flagellated stage has increased under P enrichment (gtoreq 100 mu-g SRP/L), suggesting a stimulatory role of nutrients. **Pfiesteria** -like dinoflagellates have been tracked to fish kill sites in eutrophic estuaries from Delaware Bay through the Gulf Coast. Our data point to a critical need to characterize their chronic effects on human health as well as fish recruitment, disease resistance, and survival.

2/7/11 (Item 11 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

11804761 BIOSIS Number: 98404761
Discovery of the "phantom" dinoflagellate in Chesapeake Bay
Lewitus A J; Jesien R V; Kana T M; Burkholder J M; Glasgow H B Jr; May E
Belle W. Baruch Inst. Marine Biol. Coastal Res., Baruch Marine Field Lab., Univ. S.C., PO Box 1630, Georgetown, SC 29442, USA
Estuaries 18 (2). 1995. 373-378.
Full Journal Title: Estuaries
ISSN: 0160-8347
Language: ENGLISH
Print Number: Biological Abstracts Vol. 100 Iss. 006 Ref. 082353
Since its discovery in natural estuarine habitat of North Carolina in 1991, the widespread impact of the toxic dinoflagellate, **Pfiesteria** piscicida (gen. et sp. nov.), popularly called the "phantom" dinoflagellate, on North Carolina fish stocks has been established, yet little is known about its influence outside of North Carolina estuaries. Here, we document the presence of P. piscicida in Chesapeake Bay. A fish kill was observed after inoculating an aquarium containing mummichogs with sediment samples from Jenkins Creek, a brackish creek (salinity 11 permill) of the Chesapeake Bay system. P. piscicida was the cause of the kill, as supported by morphological, physiological, and histological evidence. The appearance and behavior of the algae and symptoms associated with fish mortality were consistent with those previously observed in P. piscicida-associated aquaria fish kills in North Carolina. The discovery of P. piscicida in Chesapeake Bay supports the speculation that these toxic dinoflagellates have a dramatic and far-reaching impact on fish stocks in shallow, eutrophic estuaries along the eastern United States.

2/7/12 (Item 12 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

11771022 BIOSIS Number: 98371022
Interactions of a toxic estuarine dinoflagellate with microbial predators

and prey
Burkholder J M; Glasgow H B Jr
Dep. Botany, Box 7612, North Carolina State Univ., Raleigh, NC 27695-7612, USA
Archiv fuer Protistenkunde 145 (3-4). 1995. 177-188.
Full Journal Title: Archiv fuer Protistenkunde
ISSN: 0003-9365
Language: ENGLISH
Print Number: Biological Abstracts Vol. 100 Iss. 005 Ref. 062860
The toxic ambush-predator dinoflagellate, **Pfiesteria** piscicida (gen. et. sp. nov.) targets finfish and shellfish prey, and is a causative agent of major fish kills in representative estuaries of the southeastern United States. Live fish or their fresh tissues stimulate toxicity and gamete production and fusion, which usually occurs within a benthic or floating gelatinous mass. After fish death, remaining gametes revert to asexual, nontoxic zoospores that thrive in nutrient-enriched waters with flagellated algal prey. In the absence of fish, transformations among nontoxic flagellated, amoeboid and encysted stages in the dinoflagellate's complex life cycle are influenced by the availability of microbial prey (bacteria, algae, and microfauna including protozoan ciliates and rotifers). Three potential microbial predators of P. piscicida were identified, although one was subject to attack especially by larger amoeboid stages. The ubiquitous occurrence of flagellated and amoeboid stages in the water column and sediments of warm temperate/subtropical waters, and their voracious phagotrophy on bacterial, algal and microfaunal prey, point to a major role of toxic ambush-predator dinoflagellates in the structure and function of estuarine microbial food webs.

2/7/13 (Item 13 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

11583869 BIOSIS Number: 98183869
Response of two zooplankton grazers to an ichthyotoxic estuarine dinoflagellate
Mallin M A; Burkholder J M; Larsen L M; Glasgow H B Jr
Cent. Marine Sci. Res., Univ. N.C. Wilmington, 7205 Wrightsville Ave., Wilmington, NC 28403, USA
Journal of Plankton Research 17 (2). 1995. 351-363.
Full Journal Title: Journal of Plankton Research
ISSN: 0142-7873
Language: ENGLISH
Print Number: Biological Abstracts Vol. 099 Iss. 009 Ref. 124172
The dinoflagellate **Pfiesteria** piscicida (gen. et sp. nov.), a toxic 'ambush predator', has been implicated as a causative agent of major fish kills in estuarine ecosystems of the southeastern USA. Here we report the first experimental tests of interactions between P. piscicida and estuarine zooplankton predators, specifically the rotifer Brachionus plicatilis and the calanoid copepod Acartia tonsa. Short-term (10 day) exposure of adult B. plicatilis to P. piscicida as a food resource, alone or in combination with the non-toxic green algae Nannochloris and Tetraselmis, did not increase rotifer mortality relative to animals that were given only non-toxic greens. Similarly, short-term (3 day) feeding trials using adult A. tonsa indicated that the copepods survived equally well on either P. piscicida or the non-toxic diatom Thalassiosira pseudonana. Copepods given toxic dinoflagellates exhibited erratic behavior, however, relative to animals given diatom prey. The fecundity of B. plicatilis when fed the toxic dinoflagellate was comparable to or higher than that of rotifers fed only non-toxic greens. We conclude that, on a short-term basis, toxic

stages of P. piscicida can be readily utilized as a nutritional resource by these common estuarine zooplankters. More long-term effects of P. piscicida on zooplankton, the potential for toxin bioaccumulation across trophic levels, and the utility of zooplankton as biological control agents for this toxic dinoflagellate, remain important unanswered questions.

2/7/14 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09391075 98054650
Diagnosis of **Pfiesteria**-human illness syndrome.
Shoemaker RC
Md Med J (UNITED STATES) Nov-Dec 1997, 46 (10) p521-3, ISSN 0886-0572 Journal Code: MAN
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The first case reports of human illness caused by exposure to **Pfiesteria** piscicida toxin(s) acquired outside of a laboratory are reported. Though **Pfiesteria** , a toxin-forming dinoflagellate, is responsible for killing billions of fish in estuaries in North Carolina, its role in human illness has remained controversial, in part due to lack of identification of the toxin. A recent fish kill in the rivers of the lower Eastern Shore has permitted careful investigation and identification of a distinct clinical syndrome resulting from exposure to the **Pfiesteria** toxin--**Pfiesteria** human illness syndrome (PHIS). Patients have memory losses, cognitive impairments, headaches, skin rashes, abdominal pain, secretory diarrhea, conjunctival irritation, and bronchospasm. Not all patients have all elements of the syndrome.

2/7/15 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09391074 98054649
Toxic **Pfiesteria** and human health.
Matuszak DL; Sanders M; Taylor JL; Wasserman MP
Maryland Department of Health and Mental Hygiene, USA.
Md Med J (UNITED STATES) Nov-Dec 1997, 46 (10) p515-20, ISSN 0886-0572 Journal Code: MAN
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, MULTICASE
Toxic activity of a **Pfiesteria**-like organism occurred for much of 1997 in the waters of the lower Pocomoke River on Maryland's Eastern Shore. Maryland's experience with these toxic blooms of dinoflagellates, current knowledge of their potential human health effects, and the actions taken by state government agencies in response to a potential public health threat are reviewed. A medical diagnostic team commissioned by the Department of Health and Mental Hygiene evaluated a group of persons with intense exposures to lesioned fish or the waters from which they came and/or prominent symptoms following exposure to affected waters or lesioned fish. The principal findings of the team included consistent complaints of memory problems, acute burning of the skin following direct contact with water, and respiratory irritation. Findings on examination were limited to neurocognitive deficits in short-term memory and learning difficulties. Physicians and citizens are asked to continue to report, through their local health departments, illnesses thought to be related to exposure to lesioned fish or the waters from which they are taken. Persons with

questions or wishing to report finding lesioned fish should call the state **Pfiesteria** hotline at 1-888-584-3110. (15 Refs.)

2/7/16 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 1998 Dialog Corporation. All rts. reserv.

09305283 97478162
Results of the public health response to **Pfiesteria** workshop -- Atlanta, Georgia, September 29-30, 1997.
MMWR Morb Mortal Wkly Rep (UNITED STATES) Oct 10 1997, 46 (40) p951-2, ISSN 0149-2195 Journal Code: NE8
Languages: ENGLISH
Document type: MEETING REPORT
On September 29-30, 1997, CDC sponsored a workshop to coordinate a multistate response to public health issues about **Pfiesteria** piscicida. Workshop attendees included representatives from the health departments of eight states (Delaware, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, and West Virginia) and the District of Columbia, the U.S. Food and Drug Administration, the National Institutes of Health's National Institute of Environmental Health Sciences, CDC's National Institute for Occupational Safety and Health, and the U.S. Environmental Protection Agency.
? s au=Baden and Miami and dinoflagellate

```
              0  AU=BADEN
           2003  MIAMI
           5024  DINOFLAGELLATE
     S3       0  AU=BADEN AND MIAMI AND DINOFLAGELLATE
? s Miami and dinoflagellate

           2003  MIAMI
           5024  DINOFLAGELLATE
     S4       0  MIAMI AND DINOFLAGELLATE
? logoff

      16feb98 13:14:02 User233835 Session D75.5
           $1.80    0.030 Hrs File5
             $18.85  13 Type(s) in Format  7
          $18.85  13 Types
   $20.65  Estimated cost File5
           $0.54    0.018 Hrs File155
              $0.60  3 Type(s) in Format  7
           $0.60  3 Types
    $1.14  Estimated cost File155
           $0.95    0.007 Hrs File357
    $0.95  Estimated cost File357
           $1.20    0.010 Hrs File399
    $1.20  Estimated cost File399
           OneSearch, 4 files,  0.066 Hrs FileOS
   $23.94  Estimated cost this search
   $71.55  Estimated total session cost   0.251 Hrs.
Logoff: level 98.01.01 D  13:14:02
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Trying 9158046...Open

box200> enter system id

Logging in to Dialog

```
DIALOG INFORMATION SERVICES
PLEASE LOGON:
 ********
IALOG Invalid account number

DIALOG INFORMATION SERVICES
PLEASE LOGON:
 ********
ENTER PASSWORD:
 t8401cpq
 ********
Welcome to DIALOG

Dialog level 98.07.06D

Last logoff:  10aug98 12:03:45
Logon file001 10aug98 18:24:03
* * * NEW RATES STRUCTURE
* * * Effective June 1, connect time charges on Dialog have been
* * * eliminated and DialUnits charges have been introduced.
* * * Please check HomeBase for the text of the press release
* * * announcing this change.
* * *

* * * The ERIC Dialorder supplier now requires prepayment with
* * * all orders. For information contact ERIC document supply
* * * at 800-443-3742 or service@edrs.com.
* * *

File   1:ERIC  1966-1998/May
       (c) format only 1998 The Dialog Corporation

      Set  Items  Description
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? b 410

       10aug98 18:24:07 User233835 Session D186.1
            $0.14    0.042 DialUnits File1
     $0.14  Estimated cost File1
     $0.14  Estimated cost this search
     $0.14  Estimated total session cost   0.042 DialUnits

File 410:Chronolog(R)  1981-1998/Jul/Aug
       (c) 1998 The Dialog Corporation plc

      Set  Items  Description
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? set hi ;set hi

HILIGHT set on as ''
HILIGHT set on as ''
? b 155, 5, 399, 357, 351, 654

       10aug98 18:24:32 User233835 Session D186.2
            $0.00    0.108 DialUnits File410
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     $0.00  Estimated cost File410
     $0.00  Estimated cost this search
     $0.14  Estimated total session cost   0.150 DialUnits

SYSTEM:OS  - DIALOG OneSearch
  File 155:MEDLINE(R)  1966-1998/Sep W4
         (c) format only 1998 Dialog Corporation
  File   5:BIOSIS PREVIEWS(R)  1969-1998/JUL W4
         (c) 1998 BIOSIS
  File 399:CA SEARCH(R)  1967-1998/UD=12906
         (c) 1998 American Chemical Society
*File 399: Use is subject to the terms of your user/customer agreement.
RANK charge added; see HELP RATES 399.
  File 357:Derwent Biotechnology Abs  1982-1998/Sep B1
         (c) 1998 Derwent Publ Ltd
  File 351:DERWENT WPI  1963-1998/UD=9831;UP=9828;UM=9826
         (c)1998 Derwent Info Ltd
*File 351: All images are now present.  The display formats have
changed for 1998. See HELP FORM 351 for more information.
  File 654:US Pat.Full.  1990-1998/Aug 04
         (c) format only 1998 The Dialog Corp.
*File 654: Reassignment data now current through 05/14/98.
Reexamination, extension, expiration, reinstatement updated weekly.

      Set  Items  Description
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? s telomerase and template

           2572  TELOMERASE
          57029  TEMPLATE
      S1    229  TELOMERASE AND TEMPLATE
? rd

>>>Duplicate detection is not supported for File 351.
>>>Duplicate detection is not supported for File 654.

>>>Records from unsupported files will be retained in the RD set.
...examined 50 records  (50)
...examined 50 records  (100)
...examined 50 records  (150)
...examined 50 records  (200)
...completed examining records
      S2    137  RD (unique items)
? t s2/6/1-50


 2/6/1     (Item 1 from file: 155)
09574175   98294409
  Inhibition of human telomerase activity by peptide nucleic acids.


 2/6/2     (Item 2 from file: 155)
09554679   98245138
  Humanizing the yeast telomerase template.


 2/6/3     (Item 3 from file: 155)
09501538   98185436
  The telomere and telomerase: how do they interact?
```

2/6/4 (Item 4 from file: 155)
09498639 98217310
Effect of DNA secondary structure on human **telomerase** activity.

2/6/5 (Item 5 from file: 155)
09498597 98215641
Euplotes **telomerase** : evidence for limited base-pairing during primer elongation and dGTP as an effector of translocation.

2/6/6 (Item 6 from file: 155)
09468768 98136265
Application of **telomerase** activity for screening of primary lung cancer in broncho-alveolar lavage fluid.

2/6/7 (Item 7 from file: 155)
09461697 98167914
Interaction of recombinant Tetrahymena **telomerase** proteins p80 and p95 with **telomerase** RNA and telomeric DNA substrates.

2/6/8 (Item 8 from file: 155)
09460071 98108036
Reconstitution of human **telomerase** activity in vitro.

2/6/9 (Item 9 from file: 155)
09458296 98153767
Association of nucleoside diphosphate kinase nm23-H2 with human telomeres.

2/6/10 (Item 10 from file: 155)
09445729 98130605
A novel specificity for the primer-**template** pairing requirement in Tetrahymena **telomerase**.

2/6/11 (Item 11 from file: 155)
09440444 98147795
Flexible positioning of the **telomerase**-associated nuclease leads to preferential elimination of nontelomeric DNA.

2/6/12 (Item 12 from file: 155)
09440416 98147767
The C terminus of the major yeast telomere binding protein Rap1p enhances telomere formation.

2/6/13 (Item 13 from file: 155)
09437011 98129028
Saccharomyces cerevisiae telomeres. A review.

2/6/14 (Item 14 from file: 155)
09437008 98129025

Telomerase is an unusual RNA-containing enzyme. A review.

2/6/15 (Item 15 from file: 155)
09437007 98129024
Telomerase is a true reverse transcriptase. A review.

2/6/16 (Item 16 from file: 155)
09437006 98129023
The telomere and **telomerase**: nucleic acid-protein complexes acting in a telomere homeostasis system. A review.

2/6/17 (Item 17 from file: 155)
09432761 98108015
Mutational analysis of the Tetrahymena **telomerase** RNA: identification of residues affecting **telomerase** activity in vitro.

2/6/18 (Item 18 from file: 155)
09416784 98083184
The mouse **telomerase** RNA 5"-end lies just upstream of the **telomerase template** sequence.

2/6/19 (Item 19 from file: 155)
09406268 98103434
Evolutionary links between telomeres and transposable elements.

2/6/20 (Item 20 from file: 155)
09365462 97478563
Identification and characterization of a **telomerase** activity from Schizosaccharomyces pombe.

2/6/21 (Item 21 from file: 155)
09346124 98061107
Reconstitution of human **telomerase** with the **template** RNA component hTR and the catalytic protein subunit hTRT.

2/6/22 (Item 22 from file: 155)
09319746 97472452
Isolation of a candidate human **telomerase** catalytic subunit gene, which reveals complex splicing patterns in different cell types.

2/6/23 (Item 23 from file: 155)
09305106 98001566
Reprogramming of **telomerase** by expression of mutant **telomerase** RNA **template** in human cells leads to altered telomeres that correlate with reduced cell viability.

2/6/24 (Item 24 from file: 155)
09188913 97439819
Characterization of human **telomerase** complex.

2/6/25 (Item 25 from file: 155)
09188715 97426515
dGTP-dependent processivity and possible **template** switching of euplotes **telomerase**.

2/6/26 (Item 26 from file: 155)
09136766 97362019
Telomere maintenance without **telomerase**.

2/6/27 (Item 27 from file: 155)
09133978 97419942
Inhibition of **telomerase** activity by cisplatin in human testicular cancer cells.

2/6/28 (Item 28 from file: 155)
09091295 97357310
Variable telomeric repeat synthesis in Paramecium tetraurelia is consistent with misincorporation by **telomerase**.

2/6/29 (Item 29 from file: 155)
09006232 97274120
Telomerase activity in human urothelial tumors [see comments]

2/6/30 (Item 30 from file: 155)
08996929 97250448
A functional **telomerase** RNA swap in vivo reveals the importance of nontemplate RNA domains.

2/6/31 (Item 31 from file: 155)
08987119 97242120
Changes in **telomerase** activity and telomere length during human T lymphocyte senescence.

2/6/32 (Item 32 from file: 155)
08979728 97240763
Regulation of **telomerase** RNA **template** expression in human T lymphocyte development and activation.

2/6/33 (Item 33 from file: 155)
08947331 97197909
Block in anaphase chromosome separation caused by a **telomerase** **template** mutation [see comments]

2/6/34 (Item 34 from file: 155)
08944858 97195492
Telomerase RNA mutations in Saccharomyces cerevisiae alter **telomerase** action and reveal nonprocessivity in vivo and in vitro.

2/6/35 (Item 35 from file: 155)

08848656 97128624
Thermally induced DNA.RNA hybrid to G-quadruplex transitions: possible implications for telomere synthesis by **telomerase**.

2/6/36 (Item 36 from file: 155)
08838985 96378015
Telomerase as a potential molecular target to study G-quartet phosphorothioates.

2/6/37 (Item 37 from file: 155)
08828845 97076153
Reconstitution of human **telomerase** activity and identification of a minimal functional region of the human **telomerase** RNA.

2/6/38 (Item 38 from file: 155)
08798392 97080641
The roles of telomeres and **telomerase** in cell life span.

2/6/39 (Item 39 from file: 155)
08755317 97008069
Purification of **telomerase** from Euplotes aediculatus: requirement of a primer 3' overhang.

2/6/40 (Item 40 from file: 155)
08713844 95381063
Functional characterization and developmental regulation of mouse **telomerase** RNA.

2/6/41 (Item 41 from file: 155)
08713838 95381057
The RNA component of human **telomerase**.

2/6/42 (Item 42 from file: 155)
08712213 95343367
Telomerase in yeast.

2/6/43 (Item 43 from file: 155)
08610952 96251292
Processing of nontelomeric 3' ends by **telomerase**: default **template** alignment and endonucleolytic cleavage.

2/6/44 (Item 44 from file: 155)
08604600 96239544
A single **telomerase** RNA is sufficient for the synthesis of variable telomeric DNA repeats in ciliates of the genus Paramecium.

2/6/45 (Item 45 from file: 155)
08579499 96186701
A bulged region of the hepatitis B virus RNA encapsidation signal contains the replication origin for discontinuous first-strand DNA

synthesis.

2/6/46 (Item 46 from file: 155)
08564985 96181489
Association of the Est1 protein with **telomerase** activity in yeast.

2/6/47 (Item 47 from file: 155)
08559885 96193706
Telomerase activity is induced by the stimulation to antigen receptor in human peripheral lymphocytes.

2/6/48 (Item 48 from file: 155)
08519355 96140740
Telomere elongation observed in immortalized human fibroblasts by treatment with 60Co gamma rays or 4-nitroquinoline 1-oxide.

2/6/49 (Item 49 from file: 155)
08491048 96104555
Specific RNA residue interactions required for enzymatic functions of Tetrahymena **telomerase**.

2/6/50 (Item 50 from file: 155)
08477895 96079968
Analysis of the structure of Tetrahymena nuclear RNAs in vivo: **telomerase** RNA, the self-splicing rRNA intron, and U2 snRNA.
? t s2/6/51-100

2/6/51 (Item 51 from file: 155)
08474866 96080177
Utilization of ribonucleotides and RNA primers by Tetrahymena **telomerase**.

2/6/52 (Item 52 from file: 155)
08428530 96018820
Boundary elements of the Tetrahymena **telomerase** RNA **template** and alignment domains.

2/6/53 (Item 53 from file: 155)
08428529 96018819
Altering specific **telomerase** RNA **template** residues affects active site function.

2/6/54 (Item 54 from file: 155)
08412406 95245323
Circular rDNA replicons persist in Tetrahymena thermophila transformants synthesizing GGGGTC telomeric repeats.

2/6/55 (Item 55 from file: 155)
08300002 95258314
Ciliate **telomerase** RNA structural features.

2/6/56 (Item 56 from file: 155)
08269774 95201241
Telomere-binding proteins of Arabidopsis thaliana.

2/6/57 (Item 57 from file: 155)
08201616 95025934
TLC1: **template** RNA component of Saccharomyces cerevisiae **telomerase** [see comments]

2/6/58 (Item 58 from file: 155)
08179038 95011562
Functional reconstitution of wild-type and mutant Tetrahymena **telomerase**.

2/6/59 (Item 59 from file: 155)
08177769 94361147
Healing of broken human chromosomes by the addition of telomeric repeats.

2/6/60 (Item 60 from file: 155)
08174596 94293964
Subtelomeric chromosome instability in Plasmodium falciparum: short telomere-like sequence motifs found frequently at healed chromosome breakpoints.

2/6/61 (Item 61 from file: 155)
08168109 94105179
DNA bound by the Oxytricha telomere protein is accessible to **telomerase** and other DNA polymerases.

2/6/62 (Item 62 from file: 155)
08073450 95080257
Architecture of **telomerase** RNA.

2/6/63 (Item 63 from file: 155)
08057102 95059012
Oligonucleotides complementary to the Oxytricha nova **telomerase** RNA delineate the **template** domain and uncover a novel mode of primer utilization.

2/6/64 (Item 64 from file: 155)
08048447 95047349
Telomerase RNAs of different ciliates have a common secondary structure and a permuted **template**.

2/6/65 (Item 65 from file: 155)
07890295 94203802
The effects of nucleoside analogs on **telomerase** and telomeres in Tetrahymena.

2/6/66 (Item 66 from file: 155)
07691497 94074893
New telomeres in yeast are initiated with a highly selected subset of TG1-3 repeats.

2/6/67 (Item 67 from file: 155)
07651314 94019332
Sequence-specific DNA primer effects on **telomerase** polymerization activity.

2/6/68 (Item 68 from file: 155)
07579370 93321865
Tetrahymena **telomerase** catalyzes nucleolytic cleavage and nonprocessive elongation.

2/6/69 (Item 69 from file: 155)
07512757 93212725
De novo truncation of chromosome 16p and healing with (TTAGGG)n in the alpha-thalassemia/mental retardation syndrome (ATR-16).

2/6/70 (Item 70 from file: 155)
07495883 93181240
Isolation of telomeric DNA from the filamentous fungus Podospora anserina and construction of a self-replicating linear plasmid showing high transformation frequency.

2/6/71 (Item 71 from file: 155)
07453011 92309418
Telomere end-replication problem and cell aging.

2/6/72 (Item 72 from file: 155)
07409331 91054430
Telomeres, **telomerase** and senescence.

2/6/73 (Item 73 from file: 155)
06982118 90174298
In vivo alteration of telomere sequences and senescence caused by mutated Tetrahymena **telomerase** RNAs [see comments]

2/6/74 (Item 74 from file: 155)
06981456 90140719
Functional evidence for an RNA **template** in **telomerase**.

2/6/75 (Item 75 from file: 155)
06933552 92005713
A conserved secondary structure for **telomerase** RNA.

2/6/76 (Item 76 from file: 155)
06883903 92151294

Telomeres.

2/6/77 (Item 77 from file: 155)
06818405 92035003
Developmentally programmed healing of chromosomes by **telomerase** in Tetrahymena.

2/6/78 (Item 78 from file: 155)
06784596 91375565
Recognition of a chromosome truncation site associated with alpha-thalassaemia by human **telomerase**.

2/6/79 (Item 79 from file: 155)
06784595 91375564
Telomerase primer specificity and chromosome healing.

2/6/80 (Item 80 from file: 155)
06766414 91342660
Telomerase is processive.

2/6/81 (Item 81 from file: 155)
05907260 89347633
Tetrahymena **telomerase** contains an internal RNA **template**.

2/6/82 (Item 82 from file: 155)
05897016 89097304
A telomeric sequence in the RNA of Tetrahymena **telomerase** required for telomere repeat synthesis.

2/6/83 (Item 1 from file: 5)
14197728 BIOSIS Number: 01197728
The catalytic protein subunit hTRT and the **template** RNA component hTR reconstitute human **telomerase** activity in vitro
Print Number: Biological Abstracts/RRM Vol. 050 Iss. 005 Ref. 079634

2/6/84 (Item 2 from file: 5)
14134291 BIOSIS Number: 01134291
Regulation mechanisms of mammalian **telomerase**: A review
Print Number: Biological Abstracts Vol. 105 Iss. 007 Ref. 093165

2/6/85 (Item 3 from file: 5)
14112012 BIOSIS Number: 01112012
Humanizing the yeast **telomerase template** gene TLC1
Print Number: Biological Abstracts/RRM Vol. 050 Iss. 003 Ref. 045924

2/6/86 (Item 4 from file: 5)
14103038 BIOSIS Number: 01103038
Telomerase RNA structure and function
Print Number: Biological Abstracts/RRM Vol. 050 Iss. 003 Ref. 036950

2/6/87 (Item 5 from file: 5)
13718582 BIOSIS Number: 99718582
Studies of **telomerase** action
Print Number: Biological Abstracts/RRM Vol. 049 Iss. 010 Ref. 170692

2/6/88 (Item 6 from file: 5)
13532775 BIOSIS Number: 99532775
Purification of **telomerase** from HeLa cell extract by column chromatography, quantification by RT-PCR for **telomerase** **template** RNA (hTR), and use of antisense hTR riboprobe on blots of native PAGE gels
Print Number: Biological Abstracts/RRM Vol. 049 Iss. 006 Ref. 097555

2/6/89 (Item 7 from file: 5)
13457995 BIOSIS Number: 99457995
A novel 3'-end repair mechanism in an RNA virus
Print Number: Biological Abstracts Vol. 103 Iss. 008 Ref. 113664

2/6/90 (Item 8 from file: 5)
13395179 BIOSIS Number: 99395179
A single nucleotide substitution in the Paramecium tetraurelia **telomerase** RNA **template** confers high fidelity to the enzyme in vivo
Print Number: Biological Abstracts/RRM Vol. 049 Iss. 003 Ref. 041818

2/6/91 (Item 9 from file: 5)
13395173 BIOSIS Number: 99395173
Telomerase activation during mouse mammary tumorigenesis
Print Number: Biological Abstracts/RRM Vol. 049 Iss. 003 Ref. 041812

2/6/92 (Item 10 from file: 5)
13359451 BIOSIS Number: 99359451
Thermally induced DNA cntdot RNA hybrid to G-quadruplex transitions: Possible implications for telomere synthesis by **telomerase**
Print Number: Biological Abstracts Vol. 103 Iss. 004 Ref. 047329

2/6/93 (Item 11 from file: 5)
13314972 BIOSIS Number: 99314972
The roles of telomeres and **telomerase** in cell line span
Print Number: Biological Abstracts Vol. 103 Iss. 002 Ref. 018086

2/6/94 (Item 12 from file: 5)
12191082 BIOSIS Number: 98791082
A single **telomerase** RNA is sufficient for the synthesis of variable telomeric DNA repeats in ciliates of the genus Paramecium
Print Number: Biological Abstracts Vol. 101 Iss. 011 Ref. 158274

2/6/95 (Item 13 from file: 5)
12015364 BIOSIS Number: 98615364
Telomerase biochemistry and regulation
Print Number: Biological Abstracts/RRM Vol. 048 Iss. 002 Ref. 019707

2/6/96 (Item 14 from file: 5)
11762272 BIOSIS Number: 98362272
Telomeres, **telomerase**, and immortality
Print Number: Biological Abstracts Vol. 100 Iss. 004 Ref. 054110

2/6/97 (Item 15 from file: 5)
11604012 BIOSIS Number: 98204012
Template function in the **telomerase** RNA of Tetrahymena
Print Number: Biological Abstracts/RRM Vol. 047 Iss. 005 Ref. 077675

2/6/98 (Item 16 from file: 5)
11094921 BIOSIS Number: 97294921
Studies on telomeric DNA sequences in Saccharomyces yeasts
Print Number: Biological Abstracts/RRM Vol. 046 Iss. 007 Ref. 100274

2/6/99 (Item 1 from file: 399)
DIALOG(R)File 399:(c) 1998 American Chemical Society. All rts. reserv.

Cloning and sequences of telomerase genes from Saccharomyces cerevisiae

2/6/100 (Item 2 from file: 399)
DIALOG(R)File 399:(c) 1998 American Chemical Society. All rts. reserv.

Genetic studies of telomere position effect and the identification of the telomerase template RNA in Saccharomyces cerevisiae (silencing)
? ds

Set	Items	Description
S1	229	TELOMERASE AND TEMPLATE
S2	137	RD (unique items)

? 101-137

>>>Unrecognizable Command
? t s2/6/101-137

2/6/101 (Item 3 from file: 399)
DIALOG(R)File 399:(c) 1998 American Chemical Society. All rts. reserv.

The effect of telomerase RNA template mutations on the synthesis of telomeric DNA in Paramecium tetraurelia

2/6/102 (Item 4 from file: 399)
DIALOG(R)File 399:(c) 1998 American Chemical Society. All rts. reserv.

Telomerase activation in mouse mammary tumors: lack of detectable telomere shortening and evidence for regulation of telomerase RNA with cell proliferation

2/6/103 (Item 5 from file: 399)
DIALOG(R)File 399:(c) 1998 American Chemical Society. All rts. reserv.

Diagnosis and treatment of conditions related to telomere length or telomerase activity

2/6/104 (Item 1 from file: 357)
218595 DBA Accession No.: 98-00192
New peptide nucleic acids hybridizing specifically to mammalian **telomerase** RNA - antisense oligonucleotide analog for use in therapy, and DNA probe for cancer diagnosis

2/6/105 (Item 2 from file: 357)
212498 DBA Accession No.: 97-07619
Test for **telomerase** activity in cells by incubation with substrate to form extended product - DNA probe and DNA primer for **telomerase** activity determination and use in cancer diagnosis

2/6/106 (Item 3 from file: 357)
197898 DBA Accession No.: 96-08669
Novel **telomerase** associated polynucleotides - gene cloning and expression; **telomerase**-inhibitor and **telomerase**-activator drug screening method; diagnostic DNA probe hybridization

2/6/107 (Item 1 from file: 351)
011536166
WPI Acc No: 97-512647/199747
Title Terms: NEW; PEPTIDE; NUCLEIC; ACID; HYBRID; MAMMAL; RNA; INHIBIT; TREAT; TUMOUR; PROLIFERATION; DISEASE; DIAGNOSE

2/6/108 (Item 1 from file: 654)
02809799
ASSAYS FOR THE DNA COMPONENT OF HUMAN **TELOMERASE**
FULL TEXT: 3047 lines

2/6/109 (Item 2 from file: 654)
02803508
TELOMERASE INHIBITORS
FULL TEXT: 1319 lines

2/6/110 (Item 3 from file: 654)
02803324
HUMAN **TELOMERASE**
FULL TEXT: 933 lines

2/6/111 (Item 4 from file: 654)
02800059
TELOMERASE INHIBITORS
FULL TEXT: 1458 lines

2/6/112 (Item 5 from file: 654)
02792547
TELOMERASE INHIBITORS

FULL TEXT: 1770 lines

2/6/113 (Item 6 from file: 654)
02779105
HUMAN **TELOMERASE** RNA INTERACTING PROTEIN GENE
FULL TEXT: 960 lines

2/6/114 (Item 7 from file: 654)
02773119
METHODS FOR MEASURING TELOMERE LENGTH
FULL TEXT: 593 lines

2/6/115 (Item 8 from file: 654)
02764628
TELOMERE REPEAT BINDING FACTOR AND DIAGNOSTIC AND THERAPEUTIC USE THEREOF
FULL TEXT: 2007 lines

2/6/116 (Item 9 from file: 654)
02740195
OLIGORIBONUCLEOTIDE ASSAYS FOR NOVEL ANTIBIOTICS
FULL TEXT: 1215 lines

2/6/117 (Item 10 from file: 654)
02735266
THERAPY AND DIAGNOSIS OF CONDITIONS RELATED TO TELOMERE LENGTH AND/OR **TELOMERASE** ACTIVITY
[Diagnosis/treatment of proliferative diseases]
FULL TEXT: 2486 lines

2/6/118 (Item 11 from file: 654)
02729940
TELOMERASE INHIBITORS
[Treating cancer]
FULL TEXT: 1781 lines

2/6/119 (Item 12 from file: 654)
02724861
MODIFIED RIBOZYMLS
[Rna molecule containing modified nucloside]
FULL TEXT: 1147 lines

2/6/120 (Item 13 from file: 654)
02724860
YEAST **TELOMERASE** COMPOSITIONS
FULL TEXT: 7270 lines

2/6/121 (Item 14 from file: 654)
02721786
TELOMERASE ACTIVITY ASSAYS FOR DIAGNOSING PATHOGENIC INFECTIONS
FULL TEXT: 4620 lines

2/6/122 (Item 15 from file: 654)
02718999
METHODS FOR CANCER DIAGNOSIS AND PROGNOSIS
[Analyzing for **telomerase** activity in sample]
FULL TEXT: 1798 lines

2/6/123 (Item 16 from file: 654)
02710965
METHODS FOR SCREENING FOR AGENTS WHICH MODULATE TELOMERE LENGTH
FULL TEXT: 2429 lines

2/6/124 (Item 17 from file: 654)
02695757
MODIFIED RIBOZYMES
[Genetic engineered RNA molecule, atleast one modified nucleoside having a halo, amino, mono or disubstituted amino and azide modifier groups replacing hydroxy group at 2' position of dribose sugar; shows catalytic activity]
FULL TEXT: 1101 lines

2/6/125 (Item 18 from file: 654)
02685023
RIBOZYMES WITH RNA PROTEIN BINDING SITE
FULL TEXT: 1511 lines

2/6/126 (Item 19 from file: 654)
02677761
TELOMERASE INHIBITORS
[Anticancer, antitumor agents]
FULL TEXT: 1450 lines

2/6/127 (Item 20 from file: 654)
02668240
TELOMERASE DIAGNOSTIC METHODS
[CANCER]
FULL TEXT: 1572 lines

2/6/128 (Item 21 from file: 654)
02665738
THERAPY AND DIAGNOSIS OF CONDITIONS RELATED TO TELOMERE LENGTH AND/OR **TELOMERASE** ACTIVITY
FULL TEXT: 5702 lines

2/6/129 (Item 22 from file: 654)
02663344
SYNTHETIC OLIGONUCLEOTIDES WHICH MIMIC TELOMERIC SEQUENCES FOR USE IN TREATMENT OF CANCER AND OTHER DISEASES
[Anticarcinogenic agents]
FULL TEXT: 1075 lines

2/6/130 (Item 23 from file: 654)

02658554
METHODS FOR CANCER DIAGNOSIS AND PROGNOSIS
[Using **telomerase** concentration]
FULL TEXT: 1405 lines

2/6/131 (Item 24 from file: 654)
02656420
NORMALIZED CDNA LIBRARIES
[Genetic engineering]
FULL TEXT: 1987 lines

2/6/132 (Item 25 from file: 654)
02647322
TELOMERASE ACTIVITY ASSAYS
FULL TEXT: 1693 lines

2/6/133 (Item 26 from file: 654)
02598691
MAMMALIAN **TELOMERASE**
[Isolated, purified recombinant nucleic acid fragment comprising oligonucleotide having sequence complementary or identical to human genomic DNA sequence encoding RNA component of human **telomerase**]
FULL TEXT: 1679 lines

2/6/134 (Item 27 from file: 654)
02495931
THERAPY AND DIAGNOSIS OF CONDITIONS RELATED TO TELOMERE LENGTH AND/OR **TELOMERASE** ACTIVITY
[Detecting cancer in humans by determining whether oligonucleotide primer is extended when incubated with cell sample, nucleoside triphosphates, buffer]
FULL TEXT: 2370 lines

2/6/135 (Item 28 from file: 654)
02488516
METHOD FOR CONSTRUCTION OF NORMALIZED CDNA LIBRARIES
FULL TEXT: 2002 lines

2/6/136 (Item 29 from file: 654)
02470421
MODULATION OF PIF-1-TYPE HELICASES
[Identifying controllers of telomere formation or elongation]
FULL TEXT: 1388 lines

2/6/137 (Item 30 from file: 654)
02252121
ARTIFICIAL CHROMOSOME VECTOR
FULL TEXT: 1726 lines
? t s2/7/1-5, 8, 10, 13-18, 21, 23, 24, 27, 30-33, 36-38, 41, 52, 53, 57, 62, 63, 74-76, 81, 83, 84, 88, 97, 104-106

2/7/1 (Item 1 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

09574175 98294409
Inhibition of human **telomerase** activity by peptide nucleic acids.
Norton JC; Piatyszek MA; Wright WE; Shay JW; Corey DR
Howard Hughes Medical Institute, Department of Pharmacology, University of Texas Southwestern Medical Center at Dallas 75235, USA.
Nat Biotechnol (UNITED STATES) May 1996, 14 (5) p615-9, ISSN 1087-0156 Journal Code: CQ3
Contract/Grant No.: AG07792, AG, NIA
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We report the inhibition of human **telomerase** activity by peptide nucleic acids (PNAs). PNAs recognize the RNA component of human **telomerase** (hTR) and inhibit activity of the enzyme with IC50 values in the picomolar to nanomolar range. Inhibition depends on targeting exact functional boundaries of the hTR **template** and is 10- to 50-fold more efficient than inhibition by analogous phosphorothioate (PS) oligomers. In contrast to high selectivity of inhibition by PNAs, PS oligomers inhibit **telomerase** in a non-sequence-selective fashion. These results demonstrate that PNAs can control the enzymatic activity of ribonucleoproteins and possess important advantages relative to PS oligomers in both the affinity and the specificity of their recognition. These observations should facilitate the development of effective inhibitors of **telomerase** activity and affinity probes of **telomerase** structure.

2/7/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09554679 98245138
Humanizing the yeast **telomerase template**.
Henning KA; Moskowitz N; Ashlock MA; Liu PP
Genetics and Molecular Biology Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD 20892-4442, USA.
Proc Natl Acad Sci U S A (UNITED STATES) May 12 1998, 95 (10) p5667-71, ISSN 0027-8424 Journal Code: PV3
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Saccharomyces cerevisiae contains an irregular telomere sequence (TG1-3)n, which differs from the regular repeat (TTAGGG)n found at the telomeres of higher organisms including humans. We have modified the entire 16-nt **template** region of the S. cerevisiae **telomerase** RNA gene (TLC1) to produce (TTAGGG)n repeats, the human telomere sequence. Haploid yeast strains with the tlc1-human allele are viable with no growth retardation and express the humanized gene at a level comparable to wild type. Southern hybridization demonstrates that (TTAGGG)n repeats are added onto the yeast chromosome ends in haploid strains with the tlc1-human allele, and sequencing of rescued yeast artificial chromosome ends has verified the addition of human telomeric repeats at the molecular level. These data suggest that the irregularity of the yeast telomere sequence is because of the **template** sequence of the yeast **telomerase** RNA. Haploid strains with the tlc1-human allele will provide an important tool for studying the function of **telomerase** and its regulation by telomere-binding proteins, and these strains will serve as good hosts for human artificial chromosome assembly and propagation.

2/7/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09501538 98185436
The telomere and **telomerase**: how do they interact?
Blackburn E; Bhattacharyya A; Gilley D; Kirk K; Krauskopf A; McEachern M; Prescott J; Ware T
Department of Microbiology and Immunology, University of California, San Francisco 94143-0414, USA.
Ciba Found Symp (NETHERLANDS) 1997, 211 p2-13; discussion 15-9, ISSN 0300-5208 Journal Code: D7X
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
The tandemly repeated DNA sequence of telomeres is typically specified by the ribonucleoprotein enzyme **telomerase**. **Telomerase** copies part of its intrinsic RNA moiety to make one strand of the telomeric repeat DNA. Recent work has led to the concept of a telomere homeostasis system. We have been studying two key physical components of this system: the telomere itself and **telomerase**. Mutating the **template** sequence of **telomerase** RNA caused various phenotypes: (1) mutating specific residues in the ciliate Tetrahymena and two yeasts showed that they are required for critical aspects of **telomerase** action; (2) certain mutated telomeric sequences caused a previously unreported phenotype, i.e. a strong anaphase block in Tetrahymena micronuclei; and (3) certain **template** mutations in the **telomerase** RNA gene of the yeast Kluyveromyces lactis led to unregulated telomere elongation, which in some cases was directly related to loss of binding to K. lactis Rap1p. Using K. lactis carrying alterations in the genes for Rap1p and other silencing components, we proposed a general model for telomere length homeostasis: namely, that the structure and DNA length of the DNA-protein complex that comprises the telomere are key determinants of **telomerase** access, and hence the frequency of action of **telomerase**, at the telomere. (41 Refs.)

2/7/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09498639 98217310
Effect of DNA secondary structure on human **telomerase** activity.
Fletcher TM; Sun D; Salazar M; Hurley LH
The Cancer Therapy and Research Center, Institute for Drug Development, San Antonio, Texas 78245, USA. txf15@psu.edu
Biochemistry (UNITED STATES) Apr 21 1998, 37 (16) p5536-41, ISSN 0006-2960 Journal Code: A0G
Contract/Grant No.: RFA CA 9408, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Telomeres are specialized DNA-protein complexes located at the chromosome ends. The guanine-rich telomeric sequences have the ability to form G-quadruplex structures under physiological ionic conditions in vitro. Human telomeres are maintained through addition of TTAGGG repeats by the enzyme **telomerase** . To determine a correlation between DNA secondary structure and human **telomerase**, **telomerase** activity in the presence of various metal cations was monitored. **Telomerase** synthesized a larger proportion of products corresponding to four, five, eight, and nine full repeats of TTAGGG in 100 mM K+ and to a lesser extent

in 100 mM Na+ when a d(TTAGGG)3 input primer was used. A more even product distribution was observed when the reaction mixture contained no added Na+ or K+. Increasing concentrations of Cs+ resulted in a loss of processivity but not in the distinct manner observed in K+. When the input primer contained 7-deaza-dG, the product distribution resembled that of reactions without K+ even in the presence of 100 mM K+. Native polyacrylamide gel electrophoresis indicated that d(TTAGGG)4, d(TTAGGG)5, d(TTAGGG)8, and d(TTAGGG)9 formed compact structures in the presence of K+. The oligonucleotide d(TTAGGG)4 had a UV spectrum characteristic of that of the G-quadruplex only in the presence of K+ and Na+. A reasonable explanation for these results is that four, five, eight, and nine repeats of TTAGGG form DNA secondary structures which promote dissociation of the primer from **telomerase**. This suggests that **telomerase** activity in cells can be modulated by the secondary structure of the DNA **template**. These findings are of probable relevance to the concept of **telomerase** as a therapeutic target for drug design.

2/7/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09498597 98215641
Euplotes **telomerase** : evidence for limited base-pairing during primer elongation and dGTP as an effector of translocation.
Hammond PW; Cech TR
Department of Chemistry and Biochemistry, Howard Hughes Medical Institute, University of Colorado, Boulder, Colorado 80309-0215, USA.
Biochemistry (UNITED STATES) Apr 14 1998, 37 (15) p5162-72, ISSN 0006-2960 Journal Code: A0G
Contract/Grant No.: GM28039, GM, NIGMS
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The telomeric sequence repeats at the ends of eukaryotic chromosomes are maintained by the ribonucleoprotein enzyme **telomerase**. Telomeric DNA primers are bound by **telomerase** both at the active site, which includes base-pairing with the RNA **template**, and at a second anchor site. The stabilities of Euplotes aediculatus primer-**telomerase** complexes were determined by measuring their dissociation rates (koff), using an assay involving photo-cross-linking at the anchor site. The primer length was varied, and mismatched substitutions were introduced in a systematic manner. We observed that koff does not scale with primer length as expected for accumulated primer-**template** base-pairing. This suggests that **telomerase** maintains a more-or-less constant number of base pairs, similar to the transcription bubble maintained by RNA polymerase. An upper limit was estimated by comparing the experimental koff for the primer-**telomerase** complex to that of a model DNA-RNA duplex. All the binding energy could be attributed to 10 or 11 base pairs; alternatively, there could be <10 base pairs, with the remaining energy contributed by other parts of **telomerase**. Most primers exhibited biphasic dissociation kinetics, with variations in both the amount in each phase and the rate for each phase. Since the cross-links monitored in the dissociation assay were all formed with the 5' region of the primer, the two phases may arise from different base-pairing registers with the RNA **template** , possibly representing pre- and post-translocation complexes. A shift from slow phase to fast phase dissociation was observed in the presence of dGTP, which may implicate dGTP as a positive effector of translocation.

2/7/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09460071 98108036
Reconstitution of human **telomerase** activity in vitro.
Beattie TL; Zhou W; Robinson MO; Harrington L
Ontario Cancer Institute-Amgen Institute, Department of Medical Biophysics, University of Toronto, 620 University Avenue, Toronto, Ontario, M5G 2C1, Canada.
Curr Biol (ENGLAND) Jan 29 1998, 8 (3) p177-80, ISSN 0960-9822
Journal Code: B44
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Telomerase is a ribonucleoprotein enzyme complex that adds single-stranded telomere DNA to chromosome ends [1]. The RNA component of **telomerase** contains the **template** for telomeric DNA addition and is essential for activity [1,2]. **Telomerase** proteins have been identified in ciliates, yeast and mammals [3-12]. In Saccharomyces cerevisiae, the Est2 protein is homologous to the 123 kDa reverse transcriptase subunit of Euplotes **telomerase**, and is essential for **telomerase** activity [8]. In humans, **telomerase** activity is associated with the **telomerase** RNA hTR [13], the **telomerase** RNA-binding protein TP1/TLP1 [5,12] and the TP2 protein encoded by the human EST2 homolog [12] (also known as TRT1, hEST2 or TCS1 [9-11]). The minimal complex sufficient for activity is, however, unknown. We have reconstituted human **telomerase** activity in reticulocyte lysates and find that only exogenous hTR and TP2 are required for **telomerase** activity in vitro. Recognition of **telomerase** RNA by TP2 was species specific, and nucleotides 10-159 of hTR were sufficient for **telomerase** activity. **Telomerase** activity immunoprecipitated from the reticulocyte lysate contained hTR and recombinant TP2. Substitution of conserved amino acid residues in the reverse transcriptase domain of TP2 completely abolished **telomerase** activity. We suggest that TP2 and hTR might represent the minimal catalytic core of human **telomerase**.

2/7/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09445729 98130605
A novel specificity for the primer-**template** pairing requirement in Tetrahymena **telomerase**.
Wang H; Gilley D; Blackburn EH
Department of Microbiology and Immunology, University of California, San Francisco 94143, USA.
EMBO J (ENGLAND) Feb 16 1998, 17 (4) p1152-60, ISSN 0261-4189
Journal Code: EMB
Contract/Grant No.: GM26259, GM, NIGMS
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Telomerase is a specialized reverse transcriptase with a built-in RNA **template**. Base pairing between the templating domain of **telomerase** RNA and a telomeric DNA primer is normally a characteristic of elongation of telomeric DNA. Here we demonstrate the mechanism by which Tetrahymena **telomerase** bypasses a requirement for **template** -primer pairing in order to add telomeric DNA de novo to completely non-telomeric DNA primers. We show that this reaction initiates

by copying the **template** residue at the 3' boundary of the **telomerase** RNA **template** sequence. Unexpectedly, as the RNA **template** moves through the **telomerase** catalytic center, the number of required potential Watson-Crick base pairs between RNA **template** and DNA primer increases from zero to five. We propose that this unprecedented position specificity of a base pairing potential requirement in a polymerase underlies the chromosome healing mechanism of **telomerase**, and reflects constraints inherent in an internal **template**.

2/7/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09437011 98129028
Saccharomyces cerevisiae telomeres. A review.
Pryde FE; Louis EJ
Institute of Molecular Medicine, John Radcliffe Hospital, Oxford, United Kingdom.
Biochemistry (Mosc) (RUSSIA) Nov 1997, 62 (11) p1232-41, ISSN 0006-2979 Journal Code: CSQ
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, ACADEMIC
Recent work has yielded considerable information concerning the structure and function of telomeres and their associated sequences in the budding yeast Saccharomyces cerevisiae. The structure and maintenance of telomeres depends not only on the RNA **template** and the catalytic subunit of **telomerase**, but on a number of other proteins. These include proteins involved in assessing DNA damage and cell cycle regulation. There are also non-**telomerase** mediated processes involved in the normal maintenance of telomeres. In addition to proteins involved in telomere maintenance, there are a number of other proteins involved in the chromatin structure of the region. Many of these proteins have roles in silencing, ageing, segregation and nuclear architecture. The structure of the subtelomeric regions has been well characterized and consists of a mosaic of repeats found in variable copy numbers and locations. Amidst the variable mosaic elements there are small conserved sequences found at all ends that may have functional roles. Recent work shows that the subtelomeric repeats can rescue chromosome ends when **telomerase** fails, buffer subtelomerically located genes against transcriptional silencing, and protect the genome from deleterious rearrangements due to ectopic recombination. Thus the telomeres of yeast have a variety of roles in the life of the yeast cell beyond the protection of the ends and overcoming the end replication problem associated with linear molecules. (106 Refs.)

2/7/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09437008 98129025
Telomerase is an unusual RNA-containing enzyme. A review.
Dokudovskaya SS; Petrov AV; Dontsova OA; Bogdanov AA
School of Chemistry, Lomonosov Moscow State University, Russia.
Biochemistry (Mosc) (RUSSIA) Nov 1997, 62 (11) p1206-15, ISSN 0006-2979 Journal Code: CSQ
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
Telomeres, the natural ends of linear eukaryotic chromosomes, are

essential for protecting chromosomes from degradation and fusion. The synthesis of telomere DNA repeats in most eukaryotes is performed by a special enzyme, **telomerase**. **Telomerase** , a ribonucleoprotein enzyme, is a specialized reverse transcriptase utilizing its RNA moiety as a **template** for synthesis of telomeric DNA. Enzymatic properties and results of comparative analysis of **telomerase** RNA and protein structures from different eukaryotic systems are discussed in this review. (80 Refs.)

2/7/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09437007 98129024
Telomerase is a true reverse transcriptase. A review.
Cech TR; Nakamura TM; Lingner J
Department of Chemistry and Biochemistry, Howard Hughes Medical Institute, University of Colorado, Boulder 80309-0215, USA.
Biochemistry (Mosc) (RUSSIA) Nov 1997, 62 (11) p1202-5, ISSN 0006-2979 Journal Code: CSQ
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
Synthesis of telomeric repeats at chromosome ends requires **telomerase** , a ribonucleoprotein enzyme. The RNA subunit, which contains the **template** for DNA synthesis, has been identified in many organisms. Recently, the protein subunit that catalyzes telomeric DNA extension has also been identified in Euplotes aediculatus and Saccharomyces cerevisiae. It has sequence and functional characteristics of a reverse transcriptase related to retrotransposon and retroviral reverse transcriptases, so this new family of **telomerase** subunits has been named TRT (**Telomerase** Reverse Transcriptase). We find it remarkable that the same type of protein structure required for retroviral replication is now seen to be essential for normal chromosome telomere replication in diverse eukaryotes. (37 Refs.)

2/7/16 (Item 16 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09437006 98129023
The telomere and **telomerase**: nucleic acid-protein complexes acting in a telomere homeostasis system. A review.
Blackburn EH
Department of Microbiology and Immunology, University of California, San Francisco 94143-0414, USA. porter@itsa.ucsf.edu
Biochemistry (Mosc) (RUSSIA) Nov 1997, 62 (11) p1196-201, ISSN 0006-2979 Journal Code: CSQ
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
The tandemly repeated DNA sequence of telomeres is typically specified by the ribonucleoprotein enzyme **telomerase**. **Telomerase** copies part of its intrinsic RNA moiety to synthesize one strand of the telomeric repeat DNA Recent work, taken together with many observations over the past years, has led to the concept of a telomere homeostasis system. We have analyzed the interplay between two key physical components of this system: structural components of the telomere itself and of **telomerase**. Here we review some of these recent studies. The experimental method used in common in these studies was to make mutations in the **template**

sequence of **telomerase** RNA, which caused various phenotypes. First, mutating specific residues in the ciliate Tetrahymena thermophila and yeast showed that these residues are required for critical aspects of the enzymatic action of **telomerase** . Second, certain mutated telomeric sequences caused a strong anaphase block in Tetrahymena micronuclei. Third, specific **template** mutations in the **telomerase** RNA gene led to varying degrees of telomere elongation in Tetrahymena and the yeast Kluyveromyces lactis. For some of the K. lactis mutations, the loss of length unregulated elongation was directly related to loss of binding to K. lactis Rap 1p protein. Using K. lactis carrying alterations in the **telomerase** RNA **template** , and in the gene encoding the Rap 1p protein, we found that a crucial determinant of telomere length homeostasis is the nature of the duplex DNA-Rap 1p protein complex on the very end repeat of the telomere. We propose that this complex plays a key role in regulating access of **telomerase** to the telomere. (49 Refs.)

2/7/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09432761 98108015
Mutational analysis of the Tetrahymena **telomerase** RNA: identification of residues affecting **telomerase** activity in vitro.
Autexier C; Greider CW
Cold Spring Harbor Laboratory, PO Box 100, Cold Spring Harbor, NY 11724, USA.
Nucleic Acids Res (ENGLAND) Feb 1 1998, 26 (3) p787-95, ISSN 0305-1048 Journal Code: O8L
Contract/Grant No.: GM43080, GM, NIGMS
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Telomere-specific repeat sequences are essential for chromosome end stability. **Telomerase** maintains telomere length by adding sequences de novo onto chromosome ends. The **template** domain of the **telomerase** RNA component dictates synthesis of species-specific telomeric repeats and other regions of the RNA have been suggested to be important for enzyme structure and/or catalysis. Using enzyme reconstituted in vitro with RNAs containing deletions or substitutions we identified nucleotides in the RNA component that are important for **telomerase** activity. Although many changes to conserved features in the RNA secondary structure did not abolish enzyme activity, levels of activity were often greatly reduced, suggesting that regions other than the **template** play a role in **telomerase** function. The **template** boundary was only altered by changes in stem II that affected the conserved region upstream of the **template** , not by changes in other regions, such as stems I, III and IV, consistent with a role of the conserved region in defining the 5' boundary of the **template**. Surprisingly, **telomerase** RNAs with substitutions or deletion of residues potentially abolishing the conserved pseudoknot structure had wild-type levels of **telomerase** activity. This suggests that this base pairing interaction may not be required for **telomerase** activity per se but may be conserved as a regulatory site for the enzyme in vivo.

2/7/18 (Item 18 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09416784 98083184

The mouse **telomerase** RNA 5"-end lies just upstream of the **telomerase template** sequence.

Hinkley CS; Blasco MA; Funk WD; Feng J; Villeponteau B; Greider CW; Herr W

Cold Spring Harbor Laboratory, 1 Bungtown Road, PO Box 100, Cold Spring Harbor, NY 11724, USA.

Nucleic Acids Res (ENGLAND) Jan 15 1998, 26 (2) p532-6, ISSN 0305-1048 Journal Code: O8L

Contract/Grant No.: CA 13106, CA, NCI

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Telomerase is a ribonucleoprotein enzyme with an essential RNA component. Embedded within the **telomerase** RNA is a **template** sequence for telomere synthesis. We have characterized the structure of the 5' regions of the human and mouse **telomerase**-RNA genes, and have found a striking difference in the location of the **template** sequence: Whereas the 5'-end of the human **telomerase** RNA lies 45 nt from the **telomerase**-RNA **template** sequence, the 5'-end of the mouse **telomerase** RNA lies just 2 nt from the **telomerase**-RNA **template** sequence. Analysis of genomic sequences flanking the 5'-end of the human and mouse **telomerase** RNA-coding sequences reveals similar promoter-element arrangements typical of mRNA-type promoters: a TATA box-like element and an upstream region containing a consensus CCAAT box. This putative promoter structure contrasts with that of the ciliate **telomerase** -RNA genes whose structure resembles RNA polymerase III U6 small nuclear RNA (snRNA) promoters. These and other comparisons suggest that, during evolution, both the RNA-polymerase specificity of **telomerase** RNA-gene promoters and, more recently, the position of the **template** sequence in the **telomerase** RNA changed.

2/7/21 (Item 21 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09346124 98061107

Reconstitution of human **telomerase** with the **template** RNA component hTR and the catalytic protein subunit hTRT.

Weinrich SL; Pruzan R; Ma L; Ouellette M; Tesmer VM; Holt SE; Bodnar AG; Lichtsteiner S; Kim NW; Trager JB; Taylor RD; Carlos R; Andrews WH; Wright WE; Shay JW; Harley CB; Morin GB

Geron Corporation, Menlo Park, California 94025, USA.

Nat Genet (UNITED STATES) Dec 1997, 17 (4) p498-502, ISSN 1061-4036 Journal Code: BRO

Contract/Grant No.: AG07992, AG, NIA; AG05747, AG, NIA

Languages: ENGLISH

Document type: JOURNAL ARTICLE

The maintenance of chromosome termini, or telomeres, requires the action of the enzyme **telomerase** , as conventional DNA polymerases cannot fully replicate the ends of linear molecules. **Telomerase** is expressed and telomere length is maintained in human germ cells and the great majority of primary human tumours. However, **telomerase** is not detectable in most normal somatic cells; this corresponds to the gradual telomere loss observed with each cell division. It has been proposed that telomere erosion eventually signals entry into senescence or cell crisis and that activation of **telomerase** is usually required for immortal cell proliferation. In addition to the human **telomerase** RNA component (hTR; ref. 11), TR1/TLP1 (refs 12, 13), a protein that is homologous to the p80 protein associated with the Tetrahymena enzyme, has been identified in humans. More recently, the human **telomerase** reverse transcriptase

(hTRT; refs 15, 16), which is homologous to the reverse transcriptase (RT)-like proteins associated with the Euplotes aediculatus (Ea p123), Saccharomyces cerevisiae (Est2p) and Schizosaccharomyces pombe (5pTrt1) telomerases, has been reported to be a **telomerase** protein subunit. A catalytic function has been demonstrated for Est2p in the RT-like class but not for p80 or its homologues. We now report that in vitro transcription and translation of hTRT when co-synthesized or mixed with hTR reconstitutes **telomerase** activity that exhibits enzymatic properties like those of the native enzyme. Single amino-acid changes in conserved **telomerase** -specific and RT motifs reduce or abolish activity, providing direct evidence that hTRT is the catalytic protein component of **telomerase**. Normal human diploid cells transiently expressing hTRT possessed **telomerase** activity, demonstrating that hTRT is the limiting component necessary for restoration of **telomerase** activity in these cells. The ability to reconstitute **telomerase** permits further analysis of its biochemical and biological roles in cell aging and carcinogenesis.

2/7/23 (Item 23 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09305106 98001566
Reprogramming of **telomerase** by expression of mutant **telomerase** RNA **template** in human cells leads to altered telomeres that correlate with reduced cell viability.
Marusic L; Anton M; Tidy A; Wang P; Villeponteau B; Bacchetti S
Department of Pathology, McMaster University, Hamilton, Ontario, Canada.
Mol Cell Biol (UNITED STATES) Nov 1997, 17 (11) p6394-401, ISSN 0270-7306 Journal Code: NGY
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Telomerase synthesizes telomeric DNA by copying the **template** sequence of its own RNA component. In Tetrahymena thermophila and yeast (G. Yu, J. D. Bradley, L. D. Attardi, and E. H. Blackburn, Nature 344:126-131, 1990; M. McEachern and E. H. Blackburn, Nature 376:403-409, 1995), mutations in the **template** domain of this RNA result in synthesis of mutant telomeres and in impaired cell growth and survival. We have investigated whether mutant **telomerase** affects the proliferative potential and viability of immortal human cells. Plasmids encoding mutant or wild-type **template** RNAs (hTRs) of human **telomerase** and the neomycin resistance gene were transfected into human cells to generate stable transformants. Expression of mutant hTR resulted in the appearance of mutant **telomerase** activity and in the synthesis of mutant telomeres. Transformed cells were not visibly affected in their growth and viability when grown as mass populations. However, a reduction in plating efficiency and growth rate and an increase in the number of senescent cells were detected in populations with mutant telomeres by colony-forming assays. These results suggest that the presence of mutant **telomerase**, even if coexpressed with the wild-type enzyme, can be deleterious to cells, likely as a result of the impaired function of hybrid telomeres.

2/7/24 (Item 24 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09188913 97439819
Characterization of human **telomerase** complex.

Ramakrishnan S; Sharma HW; Farris AD; Kaufman KM; Harley JB; Collins K; Pruijn GJ; van Venrooij WJ; Martin ML; Narayanan R
Department of Oncology, Hoffmann-La Roche, 340 Kingsland Street, Nutley, NJ 07110, USA.
Proc Natl Acad Sci U S A (UNITED STATES) Sep 16 1997, 94 (19) p10075-9, ISSN 0027-8424 Journal Code: PV3
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Telomerase, a ribonucleoprotein complex, adds hexameric repeats called "telomeres" to the growing ends of chromosomal DNA. Characterization of mammalian **telomerase** has been elusive because of its low level of expression. We describe a bioinformatics approach to enrich and characterize the human **telomerase** complex. Using local sequence homology search methods, we detected similarity of the Tetrahymena p80 subunit of **telomerase** with the autoantigen Ro60. Antibodies to Ro60 immunoprecipitated the **telomerase** activity. Ro60 and p80 proteins were cross-recognizable by antibodies to either protein. **Telomerase** activity and the RNA component of **telomerase** complex were localized to a doublet in a native gel from the Ro60 antibody-precipitated material. The enriched material showed specific binding to a TTA GGG probe in vitro in an RNA **template**-dependent manner. Polyclonal antibodies to the doublet also immunoprecipitated the **telomerase** activity. These results suggest an evolutionary conservation of the **telomerase** proteins.

2/7/27 (Item 27 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09133978 97419942
Inhibition of **telomerase** activity by cisplatin in human testicular cancer cells.
Burger AM; Double JA; Newell DR
Clinical Oncology Unit, University of Bradford, West Yorkshire, U.K.
Eur J Cancer (ENGLAND) Apr 1997, 33 (4) p638-44, ISSN 0959-8049 Journal Code: ARV
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Telomerase, a ribonucleoprotein, elongates and/or maintains telomeres by adding TTAGGG tandem repeat sequences using the RNA component of the enzyme as a **template**. Enzyme activity appears to be associated with cell immortalisation and malignant progression as **telomerase** activity has been found in the majority of human tumours, but not in most somatic cells or tissues. **Telomerase** inhibition has, therefore, been proposed as a novel and potentially selective target for therapeutic intervention. Since telomeric tandem repeats as well as the human **telomerase** RNA component (hTR) and its gene are guanosine-rich, we examined whether the sequence specific, G-Pt-G, cross-linking agent cisplatin is capable of inhibiting **telomerase** activity. The TRAP assay was used to measure **telomerase** activity in cisplatin treated cell extracts and RT-PCR strategies used to examine hTR expression after drug exposure. Cisplatin reduced **telomerase** activity in a specific and concentration-dependent manner in human testicular tumour cells, whilst doxorubicin, bleomycin, methotrexate, melphalan and transplatin had no effect. It is proposed that **telomerase** inhibition might be a component of the efficacy of cisplatin in the treatment of testicular cancer.

2/7/30 (Item 30 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08996929 97250448
A functional **telomerase** RNA swap in vivo reveals the importance of nontemplate RNA domains.
Bhattacharyya A; Blackburn EH
Department of Microbiology and Immunology, University of California, San Francisco 94143-0414, USA.
Proc Natl Acad Sci U S A (UNITED STATES) Apr 1 1997, 94 (7) p2823-7, ISSN 0027-8424 Journal Code: PV3
Contract/Grant No.: GM 26259, GM, NIGMS
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The ribonucleoprotein (RNP) enzyme **telomerase** is required for replication of eukaryotic chromosomal termini. The RNA moiety of **telomerase** is essential for enzyme function and provides the **template** for telomeric DNA synthesis. However, the roles of its nontemplate domains have not been explored. Here we demonstrate that a novel interspecies **telomerase** RNA swap in vivo creates a functional but aberrant **telomerase**. **Telomerase** RNA from the ciliate Glaucoma chattoni was expressed in Tetrahymena thermophila cells. The **telomerase** RNAs from these two species have almost superimposable secondary structures. The **template** region base sequence is identical in the two RNAs, but elsewhere their sequences differ by 49%. This hybrid **telomerase** RNP was enzymatically active but added only short stretches of telomeric repeat tracts in vivo and in vitro. This new enzyme also had a strong, aberrant DNA cleavage activity in vitro. Thus, molecular interactions in the RNP involving nontemplate RNA domains affect specific aspects of **telomerase** enzyme function, raising the possibility that they may regulate **telomerase** activity.

2/7/31 (Item 31 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08987119 97242120
Changes in **telomerase** activity and telomere length during human T lymphocyte senescence.
Pan C; Xue BH; Ellis TM; Peace DJ; Diaz MO
Department of Microbiology and Immunology, Stritch School of Medicine, Loyola University at Chicago, Maywood, Illinois 60153, USA.
Exp Cell Res (UNITED STATES) Mar 15 1997, 231 (2) p346-53, ISSN 0014-4827 Journal Code: EPB
Contract/Grant No.: CA49133, CA, NCI; CA60128, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
It has been proposed that telomeres shorten with every cell cycle because the normal mechanism of DNA replication cannot replicate the end sequences of the lagging DNA strand. **Telomerase**, a ribonucleoprotein enzyme that synthesizes telomeric DNA repeats at the DNA 3' ends of eukaryotic chromosomes, can compensate for such shortening, by extending the **template** of the lagging strand. **Telomerase** activity has been identified in human germline cells and in neoplastic immortal somatic cells, but not in most normal somatic cells, which senesce after a certain number of cell divisions. We and others have found that **telomerase** activity is present in normal human lymphocytes and is upregulated when the cells are activated. But, unlike the immortal cell lines, presence of

telomerase activity is not sufficient to make T cells immortal and telomeres from these cells shorten continuously during in vitro culture. After senescence, **telomerase** activity, as detected by the TRAP technique, was downregulated. A cytotoxic T lymphocyte (CTL) cell line that was established in the laboratory has very short terminal restriction fragments (TRFs). **Telomerase** activity in this cell line is induced during activation and this activity is tightly correlated with cell proliferation. The level of **telomerase** activity in activated peripheral blood T cells, the CTL cell line, and two leukemia cell lines does not correlate with the average TRF length, suggesting that other factors besides **telomerase** activity are involved in the regulation of telomere length.

2/7/32 (Item 32 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08979728 97240763
Regulation of **telomerase** RNA **template** expression in human T lymphocyte development and activation.
Weng N; Levine BL; June CH; Hodes RJ
Experimental Immunology Branch, National Cancer Institute, Bethesda, MD 20892, USA. wengn@DC10a.nci.nih.gov
J Immunol (UNITED STATES) Apr 1 1997, 158 (7) p3215-20, ISSN 0022-1767 Journal Code: IFB
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Telomeres are unique DNA-protein complexes at the terminals of chromosomes that appear to play a critical role in protecting chromosomal integrity and in maintaining cellular replicative potential. **Telomerase** is a ribonuclear protein that is capable of elongating telomeres by the addition of telomeric hexanucleotide repeats and therefore contributing to the capacity for cell replication. **Telomerase** activity is expressed in human germline cells and malignant cells, and it has recently been demonstrated that **telomerase** activity is highly regulated in normal lymphocytes at specific stages of development and activation. However, these studies have not elucidated whether **telomerase** activity is regulated at the level of specific gene expression or whether the regulation of **telomerase** RNA **template** (hTR) and/or protein components contributes to the regulation of **telomerase** activity in normal somatic cells. To characterize at a molecular level the regulation of **telomerase** expression in human T lymphocytes, we analyzed the expression of hTR during lineage development and after in vitro activation. It was found that hTR is expressed in subsets of thymocytes with strong **telomerase** activity at levels that are consistently higher (1.5 times; $p < 0.01$) than those found in peripheral blood resting T cells. In addition, hTR is up-regulated two- to fivefold in peripheral blood naive and memory CD4+ T cells after in vitro activation with anti-CD3 plus anti-CD28. These results establish that hTR expression is regulated in normal human T cells during lineage development and after activation, and indicate that regulation of hTR expression may contribute to the regulation of **telomerase** activity in normal lymphoid cells.

2/7/33 (Item 33 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08947331 97197909
Block in anaphase chromosome separation caused by a **telomerase template** mutation [see comments]
Kirk KE; Harmon BP; Reichardt IK; Sedat JW; Blackburn EH
Department of Microbiology and Immunology, University of California, San Francisco, San Francisco, CA 94143-0414, USA.
Science (UNITED STATES) Mar 7 1997, 275 (5305) p1478-81, ISSN 0036-8075 Journal Code: UJ7
Contract/Grant No.: GM26259, GM, NIGMS
Comment in Science 1997 Mar 7;275(5305):1441-3
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Telomeres are essential for chromosome stability, but their functions at specific cell-cycle stages are unknown. Telomeres are now shown to have a role in chromosome separation during mitosis. In telomeric DNA mutants of Tetrahymena thermophila, created by expression of a **telomerase** RNA with an altered **template** sequence, division of the germline nucleus was severely delayed or blocked in anaphase. The mutant chromatids failed to separate completely at the midzone, becoming stretched to up to twice their normal length. These results suggest a physical block in mutant telomere separation.

2/7/36 (Item 36 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08838985 96378015
Telomerase as a potential molecular target to study G-quartet phosphorothioates.
Sharma HW; Hsiao R; Narayanan R
Oncology Division, Roche Research Center, Hoffmann-La Roche, Inc., Nutley, NJ 07110, USA.
Antisense Nucleic Acid Drug Dev (UNITED STATES) Spring 1996, 6 (1) p3-7, ISSN 1087-2906 Journal Code: CJY
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Inhibition of gene expression by phosphorothioate oligomers is complex and involves specific and nonspecific mechanisms. Oligomers that contain a G-quartet elicit distinct effects in vitro and in vivo that are dependent on the context of the G-quartet's occurrence within a sequence. The enzyme **telomerase** , a ribonucleoprotein, has a stretch of C residues in the RNA **template** , which are used to add terminal dG-rich telomeric repeats to the ends of chromosomes. Some but not all phosphorothioates containing a G-quartet, depending on the context of occurrence, inhibited **telomerase** activity in vitro. Non-G-quartet phosphorothioates did not inhibit this activity. Activities of control enzymes, such as reverse transcriptase or taq polymerase, were not affected by the G-quartet oligomers. Neither phosphodiester nor chimeric oligomers of a G-quartet-containing oligomer were as potent inhibition of **telomerase** activity as phosphorothioate oligomers. These results may provide a molecular target to study the effects of G-quartet-containing oligomers.

2/7/37 (Item 37 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08828845 97076153
Reconstitution of human **telomerase** activity and identification of a

minimal functional region of the human **telomerase** RNA.
Autexier C; Pruzan R; Funk WD; Greider CW
Cold Spring Harbor Laboratory, NY 11724, USA.
EMBO J (ENGLAND) Nov 1 1996, 15 (21) p5928-35, ISSN 0261-4189
Journal Code: EMB
Contract/Grant No.: AG09383, AG, NIA
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Telomerase is a ribonucleoprotein that catalyzes telomere elongation through the addition of TTAGGG repeats in humans. Activation of **telomerase** is often associated with immortalization of human cells and cancer. To dissect the human **telomerase** enzyme mechanism, we developed a functional in vitro reconstitution assay. After removal of the essential 445 nucleotide human **telomerase** RNA (hTR) by micrococcal nuclease digestion of partially purified human **telomerase** , the addition of in vitro transcribed hTR reconstituted **telomerase** activity. The activity was dependent upon and specific to hTR. Using this assay, truncations at the 5' and 3' ends of hTR identified a functional region of hTR, similar in size to the full-length **telomerase** RNAs from ciliates. This region is located between positions 1-203. Furthermore, we found that residues 1-44, 5' to the **template** region (residues 46-56) are not essential for activity, indicating a minimal functional region is located between residues 44-203. Mutagenesis of full-length hTR between residues 170-179, 180-189 or 190-199 almost completely abolished the ability of the hTR to function in the reconstitution of **telomerase** activity, suggesting that sequences or structures within this 30 nucleotide region are required for activity, perhaps by binding **telomerase** protein components.

2/7/38 (Item 38 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08798392 97080641
The roles of telomeres and **telomerase** in cell life span.
Counter CM
Whitehead Institute for Biomedical Research (Weinberg Lab), Nine Cambridge Center, MA 02142-1479, USA. counter@WI.MIT.edu
Mutat Res (NETHERLANDS) Oct 1996, 366 (1) p45-63, ISSN 0027-5107
Journal Code: NNA
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, ACADEMIC
Telomeres cap and protect the ends of chromosomes from degradation and illegitimate recombination. The termini of a linear **template** cannot, however, be completely replicated by conventional DNA-dependent DNA polymerases, and thus in the absence of a mechanisms to counter this effect, telomeres of eukaryotic cells shorten every round of DNA replication. In humans and possibly other higher eukaryotes, telomere shortening may have been adopted to limit the life span of somatic cells. Human somatic cells have a finite proliferative capacity and enter a viable growth arrested state called senescence. Life span appears to be governed by cell division, not time. The regular loss of telomeric DNA could therefore serve as a mitotic clock in the senescence programme, counting cell divisions. In most eukaryotic organisms, however, telomere shortening can be countered by the de novo addition of telomeric repeats by the enzyme **telomerase**. Cells which are "immortal' such as the human germ line or tumour cell lines, established mouse cells, yeast and ciliates, all maintain a stable telomere length through the action of **telomerase**. Abolition of **telomerase** activity in such cells nevertheless results

in telomere shortening, a process that eventually destabilizes the ends of chromosomes, leading to genomic instability and cell growth arrest or death. Therefore, loss of terminal DNA sequences may limit cell life span by two mechanisms: by acting as a mitotic clock and by denuding chromosomes of protective telomeric DNA necessary for cell viability. (179 Refs.)

2/7/41 (Item 41 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08713838 95381057
The RNA component of human **telomerase**.
Feng J; Funk WD; Wang SS; Weinrich SL; Avilion AA; Chiu CP; Adams RR; Chang E; Allsopp RC; Yu J; et al
Geron Corporation, Menlo Park, CA 94025, USA.
Science (UNITED STATES) Sep 1 1995, 269 (5228) p1236-41, ISSN 0036-8075 Journal Code: UJ7
Contract/Grant No.: AG09383, AG, NIA
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Eukaryotic chromosomes are capped with repetitive telomere sequences that protect the ends from damage and rearrangements. Telomere repeats are synthesized by **telomerase**, a ribonucleic acid (RNA)-protein complex. Here, the cloning of the RNA component of human **telomerase**, termed hTR, is described. The **template** region of hTR encompasses 11 nucleotides (5'-CUAACCCUAAC) complementary to the human telomere sequence (TTAGGG)n. Germline tissues and tumor cell lines expressed more hTR than normal somatic cells and tissues, which have no detectable **telomerase** activity. Human cell lines that expressed hTR mutated in the **template** region generated the predicted mutant **telomerase** activity. HeLa cells transfected with an antisense hTR lost telomeric DNA and began to die after 23 to 26 doublings. Thus, human **telomerase** is a critical enzyme for the long-term proliferation of immortal tumor cells.

2/7/52 (Item 52 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08428530 96018820
Boundary elements of the Tetrahymena **telomerase** RNA **template** and alignment domains.
Autexier C; Greider CW
Cold Spring Harbor Laboratory, New York 11724, USA.
Genes Dev (UNITED STATES) Sep 15 1995, 9 (18) p2227-39, ISSN 0890-9369 Journal Code: FN3
Contract/Grant No.: GM43080, GM, NIGMS
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Telomerase is a DNA polymerase fundamental to the replication and maintenance of telomere sequences at chromosome ends. The RNA component of **telomerase** is essential for the synthesis of telomere repeats. In vitro, the **template** domain (5'-CAACCCCAA-3') of the Tetrahymena **telomerase** RNA dictates the addition of Tetrahymena-specific telomere repeats d(TTGGGG)n, onto the 3' end of G-rich or telomeric substrates that are base-paired with the **template** and alignment regions of the RNA. Using a reconstituted in vitro system, we determined that altering the sequence of the alignment and **template** domains affects processivity of **telomerase** without abolishing **telomerase** activity. These

results suggest that alternative **template**/alignment regions may be functional. In the ciliate **telomerase** RNAs, there is a conserved sequence 5'-(CU)GUCA-3', located two residues upstream of the **template** domain. The location and sequence of this conserved domain defined the 5' boundary of the **template** region. These data provide insights into the regulation of telomere synthesis by **telomerase**.

2/7/53 (Item 53 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08428529 96018819
Altering specific **telomerase** RNA **template** residues affects active site function.
Gilley D; Lee MS; Blackburn EH
Department of Microbiology and Immunology, University of California, San Francisco 94143-0414, USA.
Genes Dev (UNITED STATES) Sep 15 1995, 9 (18) p2214-26, ISSN 0890-9369 Journal Code: FN3
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The ribonucleoprotein enzyme **telomerase** synthesizes telomeric DNA by copying a **template** sequence in the **telomerase** RNA. We studied the functional roles of specific residues in the Tetrahymena **telomerase** RNA **template** region. Unexpectedly, mutation of certain templating residues caused dramatic effects on specific aspects of the enzyme reaction, including loss of enzymatic fidelity and premature product dissociation. None of these fundamental changes in enzymatic action are explainable by altered base-pairing between the **telomerase** RNA and DNA substrate. These influences of specific **template** bases of the **telomerase** RNA on enzymatic properties of **telomerase** provide evidence for critical roles of these RNA residues in two active site functions--fidelity and DNA substrate/enzyme interaction.

2/7/57 (Item 57 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08201616 95025934
TLC1: **template** RNA component of Saccharomyces cerevisiae **telomerase** [see comments]
Singer MS; Gottschling DE
Department of Molecular Genetics and Cell Biology, University of Chicago, IL 60637.
Science (UNITED STATES) Oct 21 1994, 266 (5184) p404-9, ISSN 0036-8075 Journal Code: UJ7
Contract/Grant No.: GM43893, GM, NIGMS; CA 14599, CA, NCI
Comment in Science 1994 Oct 21;266(5184):387-8
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Telomeres, the natural ends of linear eukaryotic chromosomes, are essential for chromosome stability. Because of the nature of DNA replication, telomeres require a specialized mechanism to ensure their complete duplication. Telomeres are also capable of silencing the transcription of genes that are located near them. In order to identify genes in the budding yeast Saccharomyces cerevisiae that are important for telomere function, a screen was conducted for genes that, when expressed in high amounts, would suppress telomeric silencing. This screen lead to the

identification of the gene TLC1 (**telomerase** component 1). TLC1 encodes the **template** RNA of **telomerase**, a ribonucleoprotein required for telomere replication in a variety of organisms. The discovery of TLC1 confirms the existence of **telomerase** in S. cerevisiae and may facilitate both the analysis of this enzyme and an understanding of telomere structure and function.

2/7/62 (Item 62 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08073450 95080257
Architecture of **telomerase** RNA.
Bhattacharyya A; Blackburn EH
Department of Microbiology and Immunology, University of California, San Francisco 94143.
EMBO J (ENGLAND) Dec 1 1994, 13 (23) p5721-3, ISSN 0261-4189 Journal Code: EMB
Contract/Grant No.: GM 26259, GM, NIGMS
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Telomerase , an essential ribonucleoprotein reverse transcriptase, adds telomeric DNA to the ends of eukaryotic chromosomes. We examined the conformational properties of the naked RNA moiety of **telomerase** from two related ciliates, Tetrahymena thermophila and Glaucoma chattoni. As well as finding evidence for features proposed previously on the basis of phylogenetic comparisons, novel conserved structural properties were revealed. Specifically, although the region around helix III was previously proposed to form a pseudoknot, our results indicate that in the naked RNA this region maintains a level of 'plasticity', probably in an equilibrium favoring one of two helices. In addition, these studies reveal that the templating domain is not entirely single-stranded as previously proposed, but is ordered due to constraints imposed by other parts of the RNA. Finally, our results suggest that the GA bulge in helix IV may introduce a structurally conserved kink. We now propose a 'two-domain' structure for the **telomerase** RNA based on function: one conformationally flexible domain, which includes the **template** and the region around helix III, involved with enzymatic function, and a second largely helical domain, including helices I and IV and the proposed kink, which may serve as a scaffold for protein binding.

2/7/63 (Item 63 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08057102 95059012
Oligonucleotides complementary to the Oxytricha nova **telomerase** RNA delineate the **template** domain and uncover a novel mode of primer utilization.
Melek M; Davis BT; Shippen DE
Department of Biochemistry and Biophysics, Texas A&M University, College Station 77843-2128.
Mol Cell Biol (UNITED STATES) Dec 1994, 14 (12) p7827-38, ISSN 0270-7306 Journal Code: NGY
Contract/Grant No.: GM49157, GM, NIGMS
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The **telomerase** reverse transcriptase uses an essential RNA subunit

as a **template** to direct telomeric DNA synthesis. The 190-nucleotide Oxytricha nova **telomerase** RNA was identified by using an oligonucleotide probe complementary to the predicted CCCCAAAA **template** . This RNA displays extensive sequence similarity to the Euplotes crassus **telomerase** RNA and carries the same 5' CAAAACCCCAAAACC 3' telomeric domain. Antisense oligonucleotides were used to map the boundaries of the functional **template** and to investigate the mechanism of primer recognition and elongation. On the basis of their ability to inhibit or to prime **telomerase**, oligonucleotides were classified into three categories. Category 1 oligonucleotides, which extended 5' of residue 42 in the RNA, abolished elongation of (T4G4)3 and (G4T4)3 primers in vitro. In contrast, oligonucleotides terminating between residues 42 and 50 (categories 2 and 3), served as efficient **telomerase** primers. We conclude that the O. nova **template** comprises residues 42 to 50 in the 190-nucleotide RNA, a different set of nucleotides than are used by the E. crassus enzyme. Category 2 primer reactions amassed short products, and their abundance could be decreased by altering the 5' sequence of the primer, consistent with the two-primer-binding-site model for **telomerase** . Category 3 primers generated a bimodal distribution of short and long products, each having a unique elongation profile. The long-product profile is inconsistent with sequence-specific primer alignment. Rather, each primer was extended by the same register of TTTTGGGG repeats, suggesting shuttling to a default position within the **template**. The parallels between **telomerase** and RNA polymerase elongation mechanisms are discussed.

2/7/74 (Item 74 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06981456 90140719
Functional evidence for an RNA **template** in **telomerase**.
Shippen-Lentz D; Blackburn EH
Department of Molecular and Cell Biology, University of California, Berkeley 94720.
Science (UNITED STATES) Feb 2 1990, 247 (4942) p546-52, ISSN 0036-8075 Journal Code: UJ7
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The RNA moiety of the ribonucleoprotein enzyme **telomerase** from the ciliate Euplotes crassus was identified and its gene was sequenced. Functional analysis, in which oligonucleotides complementary to portions of the **telomerase** RNA were tested for their ability to prime **telomerase** in vitro, showed that the sequence 5' CAAAACCCCAAA 3' in this RNA is the **template** for synthesis of telomeric TTTTGGGG repeats by the Euplotes **telomerase**. The data provide a direct demonstration of a **template** function for a **telomerase** RNA and demarcate the outer boundaries of the telomeric **template**. **Telomerase** can now be defined as a specialized reverse transcriptase.

2/7/75 (Item 75 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06933552 92005713
A conserved secondary structure for **telomerase** RNA.
Romero DP; Blackburn EH
Department of Microbiology and Immunology, University of California, San

Francisco 94143.
Cell (UNITED STATES) Oct 18 1991, 67 (2) p343-53, ISSN 0092-8674 Journal Code: CQ4
Contract/Grant No.: GM 26259, GM, NIGMS
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The RNA moiety of the ribonucleoprotein enzyme **telomerase** contains the **template** for telomeric DNA synthesis. We present a secondary structure model for **telomerase** RNA, derived by a phylogenetic comparative analysis of **telomerase** RNAs from seven tetrahymenine ciliates. The **telomerase** RNA genes from Tetrahymena malaccensis, T. pyriformis, T. hyperangularis, T. pigmentosa, T. hegewishii, and Glaucoma chattoni were cloned, sequenced, and compared with the previously cloned RNA gene from T. thermophila and with each other. To define secondary structures of these RNAs, homologous complementary sequences were identified by the occurrence of covariation among putative base pairs. Although their primary sequences have diverged rapidly overall, a strikingly conserved secondary structure was identified for all these **telomerase** RNAs. Short regions of nucleotide conservation include a block of 22 totally conserved nucleotides that contains the telomeric templating region.

2/7/76 (Item 76 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06883903 92151294
Telomeres.
Blackburn EH
Department of Microbiology and Immunology, University of California, San Francisco 94143.
Trends Biochem Sci (ENGLAND) Oct 1991, 16 (10) p378-81, ISSN 0376-5067 Journal Code: WEF
Contract/Grant No.: GM26259, GM, NIGMS; GM32565, GM, NIGMS
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
Telomeres are specialized structures at the ends of eukaryotic linear chromosomes, consisting of protein-bound tandemly repeated simple DNA sequences. Telomeric DNA is unique in that it is copied from an RNA **template** that forms part of the enzyme, **telomerase**. This review discusses the synthesis and maintenance of these unusual structures. (28 Refs.)

2/7/81 (Item 81 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05907260 89347633
Tetrahymena **telomerase** contains an internal RNA **template**.
Lamond AI
Trends Biochem Sci (ENGLAND) Jun 1989, 14 (6) p202-4, ISSN 0376-5067 Journal Code: WEF
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
(11 Refs.)

2/7/83 (Item 1 from file: 5)

DIALOG(R)File 5:BIOSIS PREVIEWS(R)

14197728 BIOSIS Number: 01197728
The catalytic protein subunit hTRT and the **template** RNA component hTR reconstitute human **telomerase** activity in vitro
Morin G B; Weinrich S L; Pruzan R; Ma L; Ouellette M; Tesmer V M; Holt S E; Bodnar A G; Lichtsteiner S; Kim N W; Trager J B; Taylor R D; Carlos R; Andrews W H; Wright W E; Shay J W; Harley C B
Geron Corporation, 230 Constitution Drive, Menlo Park, CA 94025, USA
Proceedings of the American Association for Cancer Research Annual Meeting 39 (0). 1998. 568.
Full Journal Title: 89th Annual Meeting of the American Association for Cancer Research, New Orleans, Louisiana, USA, March 28-April 1, 1998. Proceedings of the American Association for Cancer Research Annual Meeting
ISSN: 0197-016X
Language: ENGLISH
Print Number: Biological Abstracts/RRM Vol. 050 Iss. 005 Ref. 079634

2/7/84 (Item 2 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

14134291 BIOSIS Number: 01134291
Regulation mechanisms of mammalian **telomerase**: A review
Ishikawa F
Tokyo Inst. Technol., Dep. Life Sci., 4259 Nagat-suta, Midori-ku, Yokohama 226, Japan
Biochemistry (Moscow) 62 (11). 1997. 1332-1337.
Full Journal Title: Biochemistry (Moscow)
ISSN: 0006-2979
Language: ENGLISH
Print Number: Biological Abstracts Vol. 105 Iss. 007 Ref. 093165
In this review, I summarize the most recent progress in the studies on mammalian **telomerase** , especially focusing on the molecular aspects. Possible regulation mechanisms of **telomerase** activity in mammalian cells are discussed.

2/7/88 (Item 6 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

13532775 BIOSIS Number: 99532775
Purification of **telomerase** from HeLa cell extract by column chromatography, quantification by RT-PCR for **telomerase** **template** RNA (hTR), and use of antisense hTR riboprobe on blots of native PAGE gels
Frye R A
Univ. Pittsburgh, Dep. Pathol., VA Med. Cent., Pittsburgh, PA, USA
Proceedings of the American Association for Cancer Research Annual Meeting 38 (0). 1997. 503.
Full Journal Title: Eighty-eighth Annual Meeting of the American Association for Cancer Research, San Diego, California, USA, April 12-16, 1997. Proceedings of the American Association for Cancer Research Annual Meeting
ISSN: 0197-016X
Language: ENGLISH
Print Number: Biological Abstracts/RRM Vol. 049 Iss. 006 Ref. 097555

2/7/97 (Item 15 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

11604012 BIOSIS Number: 98204012
Template function in the **telomerase** RNA of Tetrahymena
Gilley D; Lee M S; Blackburn E H
Dep. Micro. Immunol., Box 0414, Univ. Calif., San Francisco, CA 94143, USA
Journal of Cellular Biochemistry Supplement 0 (19A). 1995. 209.
Full Journal Title: Keystone Symposium on Ribozymes: Basic Science and Therapeutic Applications, Breckenridge, Colorado, USA, January 15-21, 1995. Journal of Cellular Biochemistry Supplement
ISSN: 0733-1959
Language: ENGLISH
Print Number: Biological Abstracts/RRM Vol. 047 Iss. 005 Ref. 077675

2/7/104 (Item 1 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs

218595 DBA Accession No.: 98-00192 PATENT
New peptide nucleic acids hybridizing specifically to mammalian **telomerase** RNA - antisense oligonucleotide analog for use in therapy, and DNA probe for cancer diagnosis
AUTHOR: Shay J W; Wright W E; Piatyszek M A; Corey D; Norton J C
CORPORATE SOURCE: Menlo Park, CA, USA.
PATENT ASSIGNEE: Geron 1997
PATENT NUMBER: WO 9738013 PATENT DATE: 971016 WPI ACCESSION NO.: 97-512647 (9747)
PRIORITY APPLIC. NO.: US 630019 APPLIC. DATE: 960409
NATIONAL APPLIC. NO.: WO 97US5931 APPLIC. DATE: 970409
LANGUAGE: English
ABSTRACT: A new peptide nucleic acid (PNA) contains 6-25 nucleotides, which specifically hybridize to an RNA component of mammal **telomerase**, including GGG, which hybridizes to the **template** region. The PNA may have at least 1 N-terminal amine or amino acid, and a C-terminal amino acid or carboxylic acid. A protein (1-10,000 amino acids) which enhances cellular uptake of the PNA may be covalently linked to the PNA. The protein may contain the h-region of a signal peptide and the 3rd helix of Antp-HD. The PNA may be used to produce a liposome formulation for inhibition of mammal **telomerase** activity. The PNA may also be used as a DNA probe for detection of an RNA component of mammal **telomerase** in a sample, by hybridization, for diagnosis or prognosis of cancer, or for DNA fingerprinting in forensic applications (by detection of **telomerase** gene DNA polymorphisms). The PNA may be used in cancer therapy (generally as an antisense sequence). Since PNAs are uncharged, they hybridize rapidly to form thermodynamically stable duplexes with high resistance to protease and nuclease. (74pp)

2/7/105 (Item 2 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs

212498 DBA Accession No.: 97-07619 PATENT
Test for **telomerase** activity in cells by incubation with substrate to

form extended product - DNA probe and DNA primer for **telomerase** activity determination and use in cancer diagnosis
AUTHOR: Harley C B; Kim N W; Weinrich S L
CORPORATE SOURCE: Menlo Park, CA, USA.
PATENT ASSIGNEE: Geron 1997
PATENT NUMBER: WO 9715687 PATENT DATE: 970501 WPI ACCESSION NO.: 97-259038 (9723)
PRIORITY APPLIC. NO.: US 632662 APPLIC. DATE: 960415
NATIONAL APPLIC. NO.: WO 96US9669 APPLIC. DATE: 960607
LANGUAGE: English
ABSTRACT: A method for determining whether a cell sample contains **telomerase** activity is claimed, which involves: (a) collecting a cell sample or a cell extract; (b) incubating the cell sample or extract in a reaction mixture containing a **telomerase** substrate under conditions such that the **telomerase** can catalyze extension of the **telomerase** substrate by addition of telomeric repeat sequences; (c) DNA amplification of the extended **telomerase** substrate with DNA-polymerase (EC-2.7.7.7) and DNA primer (sequences specified); and (d) correlating the presence of **telomerase** activity with the presence of the extended **telomerase** substrate. Also claimed are similar methods, in which: (a) a **template** -dependent RNA-polymerase (EC-2.7.7.6) that recognizes a promoter linked to the substrate is added to the cell sample or extract and RNA copies of the extended substrate are made and detected; or (b) a cell sample or extract is collected, the substrate is immobilized and reacted with a DNA probe complementary to the extended substrate and hybridization is determined as a measure of **telomerase** activity. This method may be used in e.g. cancer diagnosis. (96pp)

2/7/106 (Item 3 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs

197898 DBA Accession No.: 96-08669 PATENT
Novel **telomerase** associated polynucleotides - gene cloning and expression; **telomerase**-inhibitor and **telomerase**-activator drug screening method; diagnostic DNA probe hybridization
AUTHOR: Gottschling D E; Singer M S
CORPORATE SOURCE: Chicago, IL, USA.
PATENT ASSIGNEE: Arch-Develop. 1996
PATENT NUMBER: WO 9612811 PATENT DATE: 960502 WPI ACCESSION NO.: 96-239169 (9624)
PRIORITY APPLIC. NO.: US 431080 APPLIC. DATE: 950428
NATIONAL APPLIC. NO.: WO 95US13801 APPLIC. DATE: 951020
LANGUAGE: English
ABSTRACT: A new DNA sequence encodes a non-ciliate e.g. yeast **telomerase** . DNA including a GT-rich sequence complementary to a non-ciliate **telomerase** RNA **template** may be attached to an affinity chromatography column to bind to a non-ciliate **telomerase** complex. The new DNA may be inserted in a vector under the control of a recombinant promoter for expression in a prokaryote or eukaryote (e.g. yeast or mammal) host cell. A **telomerase** -associated gene may be detected by hybridization of a DNA probe derived from the sequence, and this method may be used in tumor or pathogen infection diagnosis, or detection of a sperm or ovum cell in a sample. A **telomerase** gene may be identified by preparing a Drosophila melanogaster, human or yeast cell containing a chromosome with a marker (e.g. HIS3, TRP1, LYS2, LEU2, CAN1, ADE2 or URA3) proximal to a telomere, which represses marker expression, and

identifying a gene which allows marker expression. Inhibitors of the **telomerase** may be used in therapy, and the DNA has diagnostic applications. (349pp)

? t s2/3,ab/110, 11, 116, 118, 119

>>>No matching display code(s) found in file(s): 399

2/3,AB/110 (Item 3 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02803324
Utility
HUMAN **TELOMERASE**

PATENT NO.: 5,770,422
ISSUED: June 23, 1998 (19980623)
INVENTOR(s): Collins, Kathleen, Berkeley, CA (California), US (United States of America)
ASSIGNEE(s): The Regents of the University of California, (A U.S. Company or Corporation), Oakland, CA (California), US (United States of America)
[Assignee Code(s): 13234]
APPL. NO.: 8-676,974
FILED: July 08, 1996 (19960708)

FULL TEXT: 933 lines

ABSTRACT

The invention provides methods and compositions rel a human **telomerase** and related nucleic acids, including four distinct human **telomerase** subunit proteins called p140, p105, p48 and p43 having human **telomerase** -specific activity. The proteins may be produced recombinantly from transformed host cells from the disclosed **telomerase** encoding nucleic acids or purified from human cells. Also included are human **telomerase** RNA components, as well as specific, functional derivatives thereof. The invention provides isolated **telomerase** hybridization probes and primers capable of specifically hybridizing with the disclosed **telomerase** gene, **telomerase** -specific binding agents such as specific antibodies, and methods of making and using the subject compositions in diagnosis, therapy and in the biopharmaceutical industry.

2/3,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09440444 98147795
Flexible positioning of the **telomerase**-associated nuclease leads to preferential elimination of nontelomeric DNA.
Greene EC; Bednenko J; Shippen DE
Department of Biochemistry and Biophysics, Texas A&M University, College Station 77843-2128, USA.
Mol Cell Biol (UNITED STATES) Mar 1998, 18 (3) p1544-52, ISSN 0270-7306 Journal Code: NGY
Contract/Grant No.: GM49157, GM, NIGMS
Languages: ENGLISH
Document type: JOURNAL ARTICLE

In addition to a reverse transcriptase activity, **telomerase** is associated with a DNA endonuclease that removes nucleotides from a primer 3' terminus prior to telomere repeat addition. Here we examine the DNA specificity of the primer cleavage-elongation reaction carried out by the Euplotes crassus **telomerase** . We show that the primer cleavage activity copurified with the E. crassus **telomerase** polymerase, indicating that it either is an intrinsic property of **telomerase** or is catalyzed by a tightly associated factor. Using chimeric primers containing stretches of telomeric DNA that could be precisely positioned on the RNA **template** , we found that the cleavage site is more flexible than originally proposed. Primers harboring mismatches in dT tracts that aligned opposite nucleotides 37 to 40 in the RNA **template** were cleaved to eliminate the mismatched residues along with the adjacent 3' sequence. The cleaved product was then elongated to generate perfect telomeric repeats. Mismatches in dG tracts were not removed, implying that the nuclease does not track coordinately with the polymerase active site. Our data indicate that the **telomerase** -associated nuclease could provide a rudimentary proofreading function in telomere synthesis by eliminating mismatches between the DNA primer and the 5' region of the **telomerase** RNA **template**.

2/3,AB/116 (Item 9 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02740195

Utility
OLIGORIBONUCLEOTIDE ASSAYS FOR NOVEL ANTIBIOTICS

PATENT NO.: 5,712,096
ISSUED: January 27, 1998 (19980127)
INVENTOR(s): Stern, Seth, Sterling, MA (Massachusettes), US (United States of America)
Purohit, Prakash, Worcester, MA (Massachusettes), US (United States of America)
ASSIGNEE(s): University of Massachusetts Medical Center, (A U.S. Company or Corporation), Worcester, MA (Massachusetts), US (United States of America)
[Assignee Code(s): 22237]
APPL. NO.: 8-498,402
FILED: July 05, 1995 (19950705)

This application is a continuation-in-part application of U.S. Ser. No. 08-294,450, filed Aug. 23, 1994 now abandoned.

STATEMENT AS TO FEDERALLY SPONSORED RESEARCH

This invention was made with Government support under NIH grant RO1-GM48536. The Government has certain rights in the invention.

FULL TEXT: 1215 lines

ABSTRACT

The oligoribonucleotide analogs of the invention are relatively small, three-dimensional structures derived from larger parental RNA molecules. The analogs include a first nucleic acid structure including one or more

nucleotide sequences that are derived from a region of parental RNA, wherein in its native state, the region binds to a ligand, e.g., an aminoglycoside, with a parental RNA ligand binding pattern, and a second nucleic acid structure including one or more nucleotide sequences combined with the first nucleic acid structure to form the analog and provide the analog with a conformation that binds the ligand with a ligand binding pattern that is substantially identical to the parental RNA ligand binding pattern. These analogs can be used to identify novel therapeutic compounds.

02729940

Utility

TELOMERASE INHIBITORS

[Treating cancer]

PATENT NO.: 5,703,116
ISSUED: December 30, 1997 (19971230)
INVENTOR(s): Gaeta, Federico C. A., Foster City, CA (California), US (United States of America)
Galan, Adam Antoni, Richmond, CA (California), US (United States of America)
Stracker, Elaine C., Vacaville, CA (California), US (United States of America)
ASSIGNEE(s): Geron Corporation, (A U.S. Company or Corporation), Menlo Park , CA (California), US (United States of America)
[Assignee Code(s): 37860]
APPL. NO.: 8-424,813
FILED: April 18, 1995 (19950418)

NOTICE OF U.S. GOVERNMENT RIGHTS

A portion of the work described herein was funded in part by SBIR Grant No. 1 R43 CA65178-01. The U.S. Government may therefore have certain rights relating to this invention.

FULL TEXT: 1781 lines

ABSTRACT

Methods and compositions for treating cancer and other diseases in which inhibition of **telomerase** activity can ameliorate disease symptoms or prevent or treat the disease relate to compounds that are derivatives of benzo[b]thiophenes. Such compounds are characterized by the following structure: [See structure in original document] In this compound, R sub 1 is selected from the group consisting of --OR sub 7, --NR sub 8 R sub 9, --NHNR sub 10 R sub 11, --NHNHC(X sub 2)NHR sub 12, --NHSO sub 2 NR sub 8 R sub 9, --NHNHC(O)R sub 12, --NHNHSO sub 2 R sub 12 and --NHC(O)NR sub 8 R sub 9. R sub 7 -R sub 12 are selected independently from the group consisting of hydrogen, alkyl, aryl, aralkyl, heteroaryl and heteroaralkyl. X sub 1 and X sub 2 are selected independently from the group consisting of oxygen and sulfur. R sub 2 is hydrogen or halogen. R sub 3 -R sub 6 are selected independently from the group consisting of hydrogen, halogen, hydroxyl, --NR sub 8 R sub 9, nitro, cyano, alkoxyl, lower alkyl, aryl and aryloxyl.

2/3,AB/119 (Item 12 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02724861

Utility
MODIFIED RIBOZYMLS
[Rna molecule containing modified nucloside]

PATENT NO.: 5,698,687
ISSUED: December 16, 1997 (19971216)
INVENTOR(s): Eckstein, Fritz, Gottingen, DE (Germany)
Pieken, Wolfgang, Boulder, CO (Colorado), US (United States of America)
Benseler, Fritz, Gleichen/Etzborn, DE (Germany)
Olsen, David B., West Point, PA (Pennsylvania), US (United States of America)
Williams, David M., Cherry Hinton, GB (United Kingdom).England
Heindenreich, Olaf, Gottingen, DE (Germany)
ASSIGNEE(s): Max-Planck-Gesellschaft zur Forderung der Wissenschaften e V , (A Non-U.S. Company or Corporation), Gottingen, DE (Germany)
[Assignee Code(s): 53200]
APPL. NO.: 8-434,501
FILED: May 04, 1995 (19950504)
PRIORITY: PCT-EP90-01731, WO (World Intellectual Property Org), October 12, 1990 (19901012)

This is a division of application Ser. No. 07-965,411, filed as PCT-EP91-01811 Sep. 23, 1991 published as WO92-07065 Apr. 30, 1992, hereby incorporated by referrence herein in totality, including drawings.

FULL TEXT: 1147 lines

ABSTRACT

The present invention refers to an RNA molecule with catalytic activity comprising at least one modified nucleoside, wherein the hydroxy group at the 2'-position of the fibose sugar is replaced by a modifier group, selected from halo, sulfhydryl, azido, amino, monosubstituted amino, and disubstituted andno groups, a process for the preparation of modified KNA molecules and the use of modified KNA molecules as therapeutic agents and biocatalysts.
? logoff

10aug98 18:42:25 User233835 Session D186.3
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$6.80 34 Type(s) in Format 7
$0.20 1 Type(s) in Format 4 (UDF)
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$0.92 0.174 DialUnits File5
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$5.80 4 Type(s) in Format 7
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$6.72 Estimated cost File5
$0.87 0.074 DialUnits File399
$2.00 5 Type(s) in Format 6

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          $6.00  6 Types
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          $3.60  34 Types
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    $37.24  Estimated total session cost   3.150 DialUnits
Logoff: level 98.07.06 D  18:42:25


Trying 9158046...Open

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PLEASE LOGON:
?
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 ********
ENTER PASSWORD:
 ********
Password incorrect

DIALOG INFORMATION SERVICES
PLEASE LOGON:
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STN Express timed out waiting for host response.
Trying 9158046...Open

DIALOG INFORMATION SERVICES
PLEASE LOGON:
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Maximum password attempts exceeded, try again later.
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Last logoff:  30aug98 13:39:39
Logon file001 09sep98 14:19:11
ANNOUNCEMENT    ****    ANNOUNCEMENT    ****    ANNOUNCEMENT
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***CorpTech (File 559)
***Gannett News Service (File 604)
***UMI Newsstand(TM) (File 781)
***Baton Rouge Advocate (File 382)
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RELOADED
***LA Times (File 630)
***Research Centers and Services (File 115)
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REMOVED
***IAC Industry Express (File 12) - merged into IAC PROMT (file 16)
***UPI News archival (File 260)
***Federal Register (File 669 - replaced by File 180)
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File   1:ERIC  1966-1998/Jun
       (c) format only 1998 The Dialog Corporation

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File 410:Chronolog(R)  1981-1998/Sep/Oct
       (c) 1998 The Dialog Corporation plc

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? set hi ;set hi

HILIGHT set on as ''
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PLEASE ENTER A COMMAND OR BE LOGGED OFF IN 5 MINUTES
? s ((human and telomerase) or hTR)

             202  HUMAN
               0  TELOMERASE
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                0  HTR
      S1        0  ((HUMAN AND TELOMERASE) OR HTR)
? s hTR)

>>>Parentheses do not balance
? b 155, 5, 399, 357, 351, 654

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     $0.00  Estimated cost this search
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SYSTEM:OS  - DIALOG OneSearch
  File 155:MEDLINE(R)  1966-1998/Oct W5
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  File   5:BIOSIS PREVIEWS(R)  1969-1998/Sep W1
         (c) 1998 BIOSIS
*File   5: Note: file will be reloaded soon
  File 399:CA SEARCH(R)  1967-1998/UD=12910
         (c) 1998 American Chemical Society
*File 399: Use is subject to the terms of your user/customer agreement.
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  File 357:Derwent Biotechnology Abs  1982-1998/Oct B1
         (c) 1998 Derwent Publ Ltd
  File 351:DERWENT WPI  1963-1997/UD=9835;UP=9832;UM=9830
         (c)1998 Derwent Info Ltd
*File 351: All images are now present.  The display formats have
changed for 1998. See HELP FORM 351 for more information.
  File 654:US Pat.Full.  1990-1998/Sep 01
         (c) format only 1998 The Dialog Corp.
*File 654: Reassignment data now current through 05/14/98.
Reexamination, extension, expiration, reinstatement updated weekly.

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? s ((human and telomerase) or hTR)

        11133156  HUMAN
            2732  TELOMERASE
            2515  HTR
      S1    4211  ((HUMAN AND TELOMERASE) OR HTR)
? s s1 and (allele or allelic or alleles)

            4211  S1
           62383  ALLELE
           24778  ALLELIC
           72824  ALLELES
      S2      75  S1 AND (ALLELE OR ALLELIC OR ALLELES)
? rd

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...completed examining records
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        1171105  SEQUENCE
     S4      44  S3 AND SEQUENCE
? t s4/6/1-44
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4/6/1 (Item 1 from file: 155)
09554679 98245138
Humanizing the yeast **telomerase** template.
May 12 1998

4/6/2 (Item 2 from file: 155)
09405668 98100967
Molecular biology of colorectal cancer.
Sep-Oct 1997

4/6/3 (Item 3 from file: 155)
09320325 98034880
Identification and characterization of a novel de novo mutation (L346V) in the thyroid hormone receptor beta gene in a family with generalized thyroid hormone resistance.
Oct 1997

4/6/4 (Item 4 from file: 155)
09229375 96243231
The region coding for the helix termination motif and the adjacent intron 6 of the human type I hair keratin gene hHa2 contains three natural, closely spaced polymorphic sites.
Mar 1996

4/6/5 (Item 5 from file: 155)
09207220 95379817
Alterations in p53 and p16INK4 expression and telomere length during spontaneous immortalization of Li-Fraumeni syndrome fibroblasts.
Sep 1995

4/6/6 (Item 6 from file: 155)
09136873 97399435
Mini- and microsatellites.
Jun 1997

4/6/7 (Item 7 from file: 155)
08718248 96080178
Mechanisms underlying telomere repeat turnover, revealed by hypervariable variant repeat distribution patterns in the **human** Xp/Yp telomere.
Nov 1 1995

4/6/8 (Item 8 from file: 155)
08500623 96121613
Allele -specific associated polymorphism analysis: novel modification of SSCP for mutation detection in heterozygous **alleles** using the paradigm of resistance to thyroid hormone.

1995

4/6/9 (Item 9 from file: 155)
08458389 96064788
Functional analysis of a proline to serine mutation in codon 453 of the thyroid hormone receptor beta 1 gene.
Nov 1995

4/6/10 (Item 10 from file: 155)
08271957 95206786
Alterations in telomeric repeat length in lung cancer are associated with loss of heterozygosity in p53 and Rb.
Mar 2 1995

4/6/11 (Item 11 from file: 155)
07995491 94363182
Alteration in length of telomeric repeats in lung cancer.
Jul 1994

4/6/12 (Item 12 from file: 155)
07535651 93253079
Differential expression of mutant and normal beta T3 receptor **alleles** in kindreds with generalized resistance to thyroid hormone.
May 1993

4/6/13 (Item 13 from file: 155)
07490802 93169775
Characterization of a novel mutant human thyroid hormone receptor beta in a family with hereditary thyroid hormone resistance.
Jan 1993

4/6/14 (Item 14 from file: 155)
07477664 93132186
The relative expression of mutant and normal thyroid hormone receptor genes in patients with generalized resistance to thyroid hormone determined by estimation of their specific messenger ribonucleic acid products.
Jan 1993

4/6/15 (Item 15 from file: 155)
07052145 92224389
Functional properties of a novel mutant thyroid hormone receptor in a family with generalized thyroid hormone resistance syndrome.
Mar 1992

4/6/16 (Item 16 from file: 155)
07015577 92091445
Recessive inheritance of thyroid hormone resistance caused by complete deletion of the protein-coding region of the thyroid hormone receptor-beta gene.
Jan 1992

4/6/17 (Item 17 from file: 155)
06986032 90293698
Structure of the gene of tum- transplantation antigen P198: a point mutation generates a new antigenic peptide.
Jul 1 1990

4/6/18 (Item 18 from file: 155)
06846672 92077999
Characterization of an expressible nonclassical class I HLA gene.
Oct 1991

4/6/19 (Item 19 from file: 155)
06584816 90214611
Structure of the gene of tum- transplantation antigen P35B: presence of a point mutation in the antigenic **allele**.
Apr 1990

4/6/20 (Item 1 from file: 5)
7695251 BIOSIS Number: 90063251
STRUCTURE OF THE GENE OF TUM NEGATIVE TRANSPLANTATION ANTIGEN P198 A POINT MUTATION GENERATES A NEW ANTIGENIC PEPTIDE

4/6/21 (Item 1 from file: 351)
011693609
WPI Acc No: 98-110519/199810
Title Terms: NEW; OLIGO; NUCLEOTIDE; LABEL; MOLECULAR; ENERGY; TRANSFER; PAIR; COMPONENT; USEFUL; DIAGNOSE; DNA; AMPLIFY; UNIVERSAL; HAIRPIN; PRIME; CAN; CONTAMINATE; FREE; CLOSE; TUBE; SYSTEM

4/6/22 (Item 1 from file: 654)
02809799
ASSAYS FOR THE DNA COMPONENT OF HUMAN TELOMERASE
FULL TEXT: 3047 lines

4/6/23 (Item 2 from file: 654)
02803324
HUMAN TELOMERASE
FULL TEXT: 933 lines

4/6/24 (Item 3 from file: 654)
02785735
HUMAN THERAPEUTIC USES OF BPI PROTEIN PRODUCTS
FULL TEXT: 1748 lines

4/6/25 (Item 4 from file: 654)
02779105
HUMAN TELOMERASE RNA INTERACTING PROTEIN GENE
FULL TEXT: 960 lines

4/6/26 (Item 5 from file: 654)
02764628

TELOMERE REPEAT BINDING FACTOR AND DIAGNOSTIC AND THERAPEUTIC USE THEREOF
FULL TEXT: 2007 lines

4/6/27 (Item 6 from file: 654)
02740461
HUMAN THYROID HORMONE RECEPTOR
FULL TEXT: 331 lines

4/6/28 (Item 7 from file: 654)
02724860
YEAST **TELOMERASE** COMPOSITIONS
FULL TEXT: 7270 lines

4/6/29 (Item 8 from file: 654)
02721846
ISOLATED CYTOLYTIC T CELLS SPECIFIC FOR COMPLEXES OF MAGE RELATED PEPTIDES AND HLA MOLECULES
FULL TEXT: 854 lines

4/6/30 (Item 9 from file: 654)
02698336
CELL CYCLE CHECKPOINT GENES
FULL TEXT: 3385 lines

4/6/31 (Item 10 from file: 654)
02663329
HUMAN THERAPEUTIC USES OF BACTERICIDAL/PERMEABILITY INCREASING (BPI) PROTEIN PRODUCTS
[Proteins and endotoxins]
FULL TEXT: 1555 lines

4/6/32 (Item 11 from file: 654)
02632210
DNA BINDING PROTEINS INCLUDING ANDROGEN RECEPTOR
FULL TEXT: 1222 lines

4/6/33 (Item 12 from file: 654)
02629723
ISOLATED NUCLEIC ACID MOLECULES USEFUL IN DETERMINING EXPRESSION OF A TUMOR REJECTION ANTIGEN PRECURSOR
[Genetic engineering and kits for determination of gene expression]
FULL TEXT: 3438 lines

4/6/34 (Item 13 from file: 654)
02523678
POLYNUCLEOTIDES ENCODING INSECT STEROID HORMONE RECEPTOR POLYPEPTIDES AND CELLS TRANSFORMED WITH SAME
[Genetic engineering]
FULL TEXT: 3417 lines

4/6/35 (Item 14 from file: 654)

02470421
MODULATION OF PIF-1-TYPE HELICASES
[Identifying controllers of telomere formation or elongation]
FULL TEXT: 1388 lines

4/6/36 (Item 15 from file: 654)
02466268
ISOLATED NUCLEIC ACID MOLECULES WHICH ENCODE MAGE DERIVED NONAPEPTIDES
[Nonapeptides bind to human leukocyte antigens on cell surfaces leading to lysis by cytolytic T lymphocytes]
FULL TEXT: 822 lines

4/6/37 (Item 16 from file: 654)
02438663
HUMAN THYROID HORMONE RECEPTOR DNA
[Purified and isolated nucleic acid molecule which could be defined as DNA or complementarity DNA or nucleotide **sequence**]
FULL TEXT: 320 lines

4/6/38 (Item 17 from file: 654)
02402884
ISOLATED NONAPEPTIDES DERIVED FROM MAGE GENES AND USES THEREOF
[Bind to human leukocyte antigen molecule on cell to form complex which provokes lysis of cell by specific cytolytic T-cell]
FULL TEXT: 621 lines

4/6/39 (Item 18 from file: 654)
02332663
NUCLEOTIDE **SEQUENCE** ENCODING THE TUMOR REJECTION ANTIGEN PRECURSOR, MAGE-1
FULL TEXT: 1992 lines

4/6/40 (Item 19 from file: 654)
02297188
RECEPTORS: THEIR IDENTIFICATION, CHARACTERIZATION, PREPARATION AND USE
[Polypeptides, transcription, transactivation domains, hormones]
FULL TEXT: 947 lines

4/6/41 (Item 20 from file: 654)
02252121
ARTIFICIAL CHROMOSOME VECTOR
FULL TEXT: 1726 lines

4/6/42 (Item 21 from file: 654)
02243294
RECEPTORS: THEIR IDENTIFICATION, CHARACTERIZATION, PREPARATION AND USE
[Bioassay for steroid hormones, culturing test cells that contain DNA and monitoring the expression level]
FULL TEXT: 917 lines

4/6/43 (Item 22 from file: 654)
02191468

RECEPTORS: THEIR IDENTIFICATION, CHARACTERIZATION, PREPARATION AND USE
[Measuring genetic transcription induced by steroid hormone receptors bound to DNA segments for use in screening assays]
FULL TEXT: 931 lines

4/6/44 (Item 23 from file: 654)
02110184
THYROID HORMONE RECEPTOR
[Pure polypeptide deduced from cyclic DNA]
FULL TEXT: 421 lines
? t s4/3,ab/22,23

4/3,AB/22 (Item 1 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02809799
Utility
ASSAYS FOR THE DNA COMPONENT OF HUMAN TELOMERASE

PATENT NO.: 5,776,679
ISSUED: July 07, 1998 (19980707)
INVENTOR(s): Villeponteau, Bryant, San Carlos, CA (California), US (United States of America)
Feng, Junli, San Carlos, CA (California), US (United States of America)
Funk, Walter, Union City, CA (California), US (United States of America)
Andrews, William H., Richmond, CA (California), US (United States of America)
ASSIGNEE(s): Geron Corporation, (A U.S. Company or Corporation), Menlo Park , CA (California), US (United States of America)
[Assignee Code(s): 37860]
APPL. NO.: 8-482,115
FILED: June 07, 1995 (19950607)

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of copending U.S. patent application Ser. No. 08-272,102, filed 7 Jul. 1994, abandoned U.S. patent application Ser. No. 08-330,123, filed 27 Oct. 1994, now U.S. Pat. No. 5,583,016 each of which is incorporated herein by reference.

FULL TEXT: 3047 lines

ABSTRACT

Nucleic acids comprising the RNA component of a mammalian **telomerase** are useful as pharmaceutical, therapeutic, and diagnostic reagents.

4/3,AB/23 (Item 2 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02803324
Utility

HUMAN TELOMERASE

PATENT NO.: 5,770,422
ISSUED: June 23, 1998 (19980623)
INVENTOR(s): Collins, Kathleen, Berkeley, CA (California), US (United States of America)
ASSIGNEE(s): The Regents of the University of California, (A U.S. Company or Corporation), Oakland, CA (California), US (United States of America)
[Assignee Code(s): 13234]
APPL. NO.: 8-676,974
FILED: July 08, 1996 (19960708)

FULL TEXT: 933 lines

ABSTRACT

The invention provides methods and compositions rel a **human telomerase** and related nucleic acids, including four distinct **human telomerase** subunit proteins called p140, p105, p48 and p43 having **human telomerase**-specific activity. The proteins may be produced recombinantly from transformed host cells from the disclosed **telomerase** encoding nucleic acids or purified from **human** cells. Also included are **human telomerase** RNA components, as well as specific, functional derivatives thereof. The invention provides isolated **telomerase** hybridization probes and primers capable of specifically hybridizing with the disclosed **telomerase** gene, **telomerase** -specific binding agents such as specific antibodies, and methods of making and using the subject compositions in diagnosis, therapy and in the biopharmaceutical industry.

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            FTSNET   0.116 Hrs.
     $7.94  Estimated cost this search
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  *    SEPTEMBER 8, 1998 for U.S. Patent Image Data.                  *
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  *                Help Desk --> 703-305-9000                         *
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  *    related questions.                                             *
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=> s pn=5776679 or pn=5770422

             1 PN=5776679
             1 PN=5770422
L1           2 PN=5776679 OR PN=5770422

=> s l1 and (allele or alleles or allelic)

          1621 ALLELE
          1608 ALLELES
          1839 ALLELIC
L2           2 L1 AND (ALLELE OR ALLELES OR ALLELIC)

=> d kwic 1-2

US PAT NO:      **5,776,679** [IMAGE AVAILABLE]          L2: 1 of 2

SUMMARY:

BSUM(19)

 In . . . the structure or abundance of a hTR RNA of hTR gene
sequence, or which are linked to a pathognomonic hTR **allele** which can
be detected by RFLP and/or **allele**-specific PCR, or other suitable
detection method.

SUMMARY:

BSUM(21)

 The . . . gene rearrangements or amplification of the hTR gene in
cells explanted from a patient, or detection of a pathognomonic hTR
**allele** (e.g., by RFLP or **allele**-specific PCR analysis).
Typically, the detection will be by in situ hybridization using a labeled
(e.g., .sup.32 p, .sup.35 S, .sup.14. . .

SUMMARY:

BSUM(33)

 As used herein, the term "disease **allele**" refers to an **allele** of
a gene which is capable of producing a recognizable disease. A disease
**allele** may be dominant or recessive and may produce disease directly
or when present in combination with a specific genetic background or
pre-existing pathological condition. A disease **allele** may be present
in the gene pool or may be generated de novo in an individual by somatic
mutation.

DETDESC:

DETD(63)

 Within the human population there can be minor alterations in the basic
primary sequence of hTR, including **allelic** variants, restriction site
```

polymorphisms, and congenital hTR disease **alleles** associated with genetic disease.
US PAT NO: **5,770,422** [IMAGE AVAILABLE] L2: 2 of 2

SUMMARY:

BSUM(35)

In diagnosis, human telomerase hybridization probes find use in identifying wild-type and mutant human telomerase **alleles** in clinical and laboratory samples. Mutant **alleles** are used to generate **allele**-specific oligonucleotide (ASO) probes for high-throughput clinical diagnoses. In therapy, therapeutic human telomerase nucleic acids are used to modulate cellular expression. . .

SUMMARY:

BSUM(37)

In . . . Such nucleic acids may be human telomerase expression vectors, vectors which upregulate the functional expression of an endogenous human telomerase **allele**, or replacement vectors for targeted correction of human telomerase mutant **alleles**.

=> t cls 1-2

5,776,679 [IMAGE AVAILABLE]7 CLASSIFICATIONS L2: 1 of 2

1.	435/6	OR
2.	435/91.2	XR
3.	435/91.21	XR
4.	435/91.51	XR
5.	536/23.1	XR
6.	536/24.31	XR
7.	536/24.33	XR

5,770,422 [IMAGE AVAILABLE]6 CLASSIFICATIONS L2: 2 of 2

1.	435/194	OR
2.	435/252.3	XR
3.	435/320.1	XR
4.	530/350	XR
5.	530/412	XR
6.	536/23.2	XR

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ALL L# QUERIES AND ANSWER SETS ARE DELETED AT LOGOFF
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